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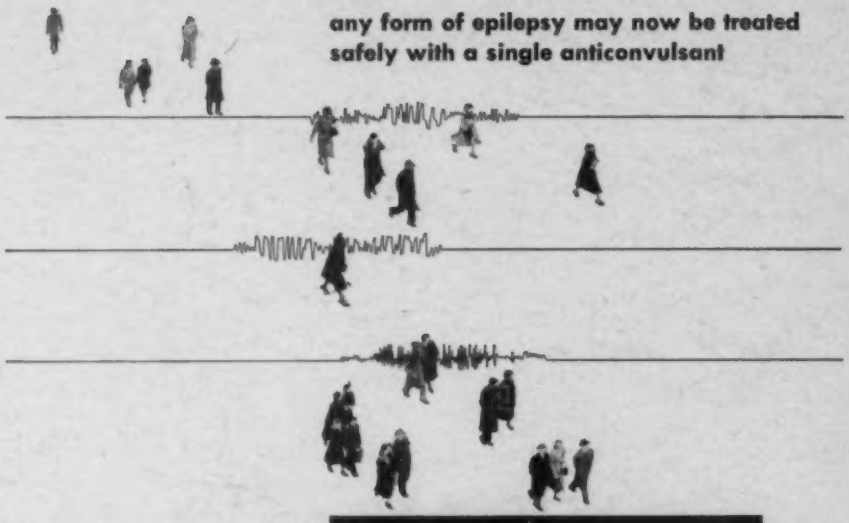

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Original Communications

A COMPARISON OF "SYMPTOMATIC TREATMENT," GAMMA GLOBULIN, AND PENICILLIN IN THE TREATMENT OF SCARLET FEVER

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THE syndrome of scarlet fever is a composite of the lesion at the portal of entry of the beta-hemolytic streptococcus and the peripheral reaction to the erythrogenic and other toxins elaborated by this organism. Until the advent of effective antibacterial agents, the treatment of this disease was directed almost entirely towards amelioration of the toxic manifestations; the local lesion was permitted to undergo its natural evolution toward uncomplicated resolution or extension either by direct spread or by hematogenous or lymphogenous dissemination. The development of drugs capable of inhibiting *Streptococcus pyogenes* has made available agents for use in the management of the bacterial phase of scarlet fever in addition to those already at hand for control of the toxic phase.

The effectiveness of various types of antisera in the reduction of the severity of the toxic manifestations of scarlet fever is so well known that it requires very little comment. Convalescent human serum and antitoxic horse serum have been shown quite conclusively to produce rapid fading of the rash and improvement in some of the other "toxic" manifestations such as abdominal pain, nausea, vomiting, headache, arthralgia, etc. There is no unequivocal evidence, however, that such antitoxins exert a beneficial effect on the lesion at the portal of entry of the organisms or reduce the incidence of suppurative or nonsuppurative complications. That these agents would have little direct antibacterial effect is to be expected. Human convalescent serum, since it is usually drawn at the end of three weeks after the onset of infection, probably contains very little if any antibacterial antibodies; these do not develop in appreciable quantities until the sixth or seventh week after infection (Kuttner,[11] Rothbard[17]). Furthermore, should serum be drawn from a human patient late in convalescence the antibacterial antibody which may be present is still type specific and active

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All of the penicillin used in this investigation was furnished by the Schenley Laboratories.

The gamma globulin used in this study has been prepared from blood collected by the American Red Cross under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University. The study was supervised by Dr. C. A. Janeway under the direction of Dr. A. R. Dochez, neither of whom, however, are necessarily responsible for the opinions expressed in this paper.

only against the serologic type responsible for the infection. The general use of such antiserums for treatment of the bacterial phase of scarlet fever is more or less precluded therefore, since, as is well known, this disease may be due to a wide variety of serologic types of the beta-hemolytic streptococcus. Antitoxins prepared in horses suffer from the same lack of antibacterial activity, possibly even to a greater degree, since the material injected for stimulation of antitoxin production is a culture filtrate which probably contains very little, if any, of the antigenic components necessary to stimulate antibacterial antibody.

Methods for the fractionation of human plasma devised by Cohen, Oncley, and Strong,[2] have made available preparations of gamma globulin which contain from three to five times as high a titer of erythrogenic antitoxin as the average human scarlet fever immune serum. Landon and Jackson,[12] and Landon and Greenfield,[13] have reported the results of investigations on the use of this type of gamma globulin in the treatment of scarlet fever. The administration of between 1,400 and 3,200 anti-erythrogenic units of this material, appeared to have a satisfactory effect on the early phase of scarlet fever and in preventing early and late complications. In a group of 238 patients with severe scarlet fever, the temperature was shown to fall to normal in forty-eight hours. This was accompanied by rapid fading of the rash. Little diminution in the severity of the sore throat was noted, however. In 81 cases treated with horse serum streptococcal antitoxin in doses of 9,000 and 27,000 units, the initial signs and symptoms of the disease responded favorably, but a considerable number of the patients developed secondary fevers on the sixth to eighth days after infection; these may have been due to serum reactions. In severe cases, little difference could be found in the incidence of septic complications in patients treated with globulin or with antitoxin. The group receiving symptomatic therapy showed twice as many suppurative sequelae as the others, however. In a study by Landon and Greenfield,[13] 245 patients with scarlet fever were treated in rotation with penicillin, gamma globulin, and horse serum streptococcal antitoxin. Three and one-half times as many complications occurred in the group treated with penicillin as in that receiving gamma globulin; patients given antitoxin showed five times as many sequelae as those injected with gamma globulin. It is quite surprising to note that in the group receiving penicillin, acute purulent otitis media, infectious arthritis, and cervical adenitis occurred in three individuals prior to the fourteenth day. Three others developed lobar pneumonia, tonsillitis, and bilateral cervical adenitis, and acute purulent otitis media on the nineteenth day. Rheumatic fever was not noted in a group of 135 with severe scarlet fever who had received gamma globulin, whereas eight instances of this disease and three of glomerular nephritis occurred in 419 cases treated symptomatically, with sulfadiazine, or with human scarlet fever immune serum. In a group of twenty-four patients with mild infections to whom gamma globulin was administered, no late complications developed, whereas in 623 mild ones receiving other forms of treatment, 16 late sequelae occurred.

The sulfonamides have been used quite widely in the treatment of scarlet fever. They have been shown to be without effect on the toxic manifestations of the disease by Wesselhoeft,[20] and by Fox and Gordon.[5] Although there is a

general impression among many clinicians that these drugs exert a definite beneficial effect on the local streptococcal lesion, there is, on the other hand, some very good evidence that the primary site of infection is not at all affected and that the incidence of suppurative complications is not reduced even with early and adequate therapy (Wesselhoeft,[20] Dingle,[3]). That there is no decrease in the incidence of such nonsuppurative sequelae as rheumatic fever or acute diffuse glomerular nephritis following the treatment of scarlet fever with one of the sulfonamides is well known. This group of agents is also not very effective in eradicating the carrier state; although temporary suppression of the growth of beta-hemolytic streptococci in the pharynx may occur while they are being administered, cessation of treatment leads to a reappearances of the organisms in most cases, a phenomenon which has been called "cultural latency" by Rubenstein and Foley.[18] Thus, all the evidence tends to indicate that the sulfonamides are not very effective in the therapy of scarlet fever. The demonstration of sulfonamide-resistant streptococci decreases, even further, the applicability of this group of drugs in the management of beta-hemolytic streptococcal infections, particularly those of the upper respiratory tract.

The antibacterial agent which has attracted the greatest attention in the last five years in the treatment of scarlet fever and other streptococcal diseases is penicillin. This antibiotic has been proved definitely to be effective against *Str. pyogenes* in vitro and its usefulness in various streptococcal infections has been very well established. A number of studies on the use of pencillin in the treatment of scarlet fever have already appeared in the literature; these are reported below in detail since later papers in this series will omit any further review of these publications.

One of the first studies of the effect of penicillin therapy in scarlet fever was that of Meads, Flipse, Barnes, and Finland[15] who showed that the administration of 10,000 units of this material every three hours intramuscularly produced rapid clearance of streptococci from the pharynx in some cases and persistence for as long as one week in others. In individuals to whom no treatment was given, the organisms remained in the throat throughout the entire course of the disease, while in those to whom sulfadiazine was administered they were reduced in number and disappeared intermittently always recurring, however, when the drug was stopped. Spraying of the nasopharynx with solutions containing 1,000 units of pencillin was found to be ineffective in eradicating streptococci from the pharynx but did rid the nose of them for as long as therapy was continued; return of the organisms was observed, however, when the antibiotic agent was omitted.

A group of twenty-eight patients with scarlet fever was studied by Plummer, Duerschner, Warren, Rogliano, and Sloan.[16] Of these, nine received 90,000 units of penicillin per day for three to four days, showed an immediated striking clinical response, but four had bacteriologic and clinical relapse within forty-eight hours after treatment was stopped. In nine individuals given 100,000 to 150,000 units of the antibiotic agent for one day only, cultures became negative in twenty-four hours but were positive again quickly in all patients but

one. In another group of ten individuals who were given 120,000 units of the antibiotic agent per day for six days, nine were cured in thirty-six hours and there were no recurrences of streptococci in the pharynx.

Epidemiology Unit No. 82 at the Naval Hospital in Treasure Island in San Francisco[4] made a study of the effect of several treatment schedules of penicillin in scarlet fever. In twenty-six patients given 240,000 units of the antibiotic agent in three days there was an incidence of 31 per cent complications and 77 per cent recurrence of positive throat cultures. In a group of forty-four patients treated with 360,000 units of penicillin in six days, the sequelae rate was reduced to 14 per cent and return of streptococci fell to 27 per cent. Increasing the quantity of penicillin to 480,000 units in eight days in forty-eight individuals resulted in a reduction of the complication rate to 6 per cent and bacteriologic relapses to only 8 per cent. No penicillin resistant strains were discovered in this study.

A comparison of penicillin X, symptomatic treatment, and sulfadiazine in the therapy of scarlet fever, by Hirsch, Dowling, and Sweet[6] revealed complications in 3 out of 34 subjects treated with penicillin, 11 out of 35 individuals receiving symptomatic treatment, and 2 out of 13 patients given sulfadiazine. The duration of fever was found to be shortest in the penicillin group and averaged 54 hours. Ashley,[1] studying the response of scarlet fever to convalescent serum, antistreptococcus serum, and penicillin concluded that the results obtained with convalescent scarlet fever serum plus penicillin were much better than those with either convalescent or antistreptococcus horse serum alone, regardless of the severity of the illness. The incidence of complications following antistreptococcal horse serum was considerably less than when convalescent human serum was used, but was lowest in the group that received penicillin together with convalescent human serum. Ashley concluded that human convalescent serum given intravenously in quantities of 50 c.c. or more within twenty-four hours of the appearance of the rash, together with penicillin (30,000 units intramuscularly on admission and 15,000 units every three hours until the temperature had been normal for five days) was the treatment of choice for scarlet fever.

Hirsh, Rotman-Kavka, Dowling, and Sweet[7] treated a group of eighty-six patients with scarlet fever with penicillin, admitting to their study only those having temperatures of 102° F. or over, evidence of pronounced toxicity, or those with a pyogenic complication. Several dosage schedules and types of penicillin were used. Controls consisted of patients who received antitoxin and those given only so-called "symptomatic" therapy. In those treated with penicillin, the incidence of bacterial complications was 7 per cent and of positive throat cultures late in the course of the disease 8 per cent; the average duration of fever was fifty-two hours. In 123 individuals treated "symptomatically," temperatures remained elevated for an average of ninety-nine hours, bacterial complications occurred in 26 per cent and 82 per cent of them still harbored beta-hemolytic streptococci in their pharynx during convalescence. In 25 patients given antitoxin, the average persistence of fever was only twenty-nine hours but the incidence of bacterial sequelae was 44 per cent and of the

late carrier state 85 per cent. Fifty patients were also treated by these investigators with 100,000 units of penicillin administered every four hours orally. In all of them fall in temperature and decrease in toxicity were prompt, beta-hemolytic streptococci disappeared from the pharynx rapidly, and none developed a pyogenic complication.

A group of 547 patients with scarlet fever were treated by Hoyne and Brown[8] by different methods; of these, 116 received penicillin, 69 had convalescent scarlet fever serum administered to them, 48 were treated with sulfonamide drugs, 2 received scarlet fever antitoxin, and 312 were given "symptomatic" therapy. These investigators found that penicillin was as effective in scarlet fever as convalescent serum and was superior to the sulfonamides. The most important attribute of the antibiotic agent was its ability to lower the rate of bacterial complications. Hoyne and Brown[8] felt, however, that unless it could be proved that penicillin was far more efficient than all other types of treatment for scarlet fever "its customary method of administration must be regarded as an obstacle to its use."

In an investigation of an epidemic of scarlet fever due entirely to sulfonamide-resistant Type 17 *Str. pyogenes*, Jennings and DeLamater[9] treated patients "symptomatically" with sulfadiazine and with penicillin. Eighty-seven patients were given the antibiotic agent. One group of eight was first treated with 4 Gm. of sulfadiazine per day for eight days with no effect on the throat cultures; on the tenth, eleventh, and twelfth days 100,000 units of penicillin were administered. All showed disappearance of streptococci from the pharynx during this period; two continued with negative cultures while six reverted to positive. The incidence of complications in this group was 37.5 per cent. In twenty-eight patients to whom 200,000 units of penicillin were given intramuscularly per day for three or four days, there was a temporary suppression of organisms in the throat during therapy, but they returned rapidly when the drug was discontinued. In this series sequelae were present in 28 per cent. In eleven individuals treated with 200,000 units of penicillin per day for two to four days followed by 100,000 units daily on the tenth, eleventh, and twelfth days of disease and by 1 Gm. of sulfadiazine daily for thirteen to eighteen days thereafter, the antibiotic substance did not cause as marked a suppression of pharyngeal streptococci as had occurred in the previous group. The second period of therapy produced a temporary suppression in three cases. Eight patients received 400,000 units of penicillin daily for three days and then 160,000 units per day for three or more days. The clinical benefits were more striking than with the smaller doses and elimination of the beta-hemolytic streptococcus from the upper respiratory tract occurred in five out of eight. In sixteen subjects treated with 400,000 units of penicillin for three days and then 200,000 units per day for two to seven days, there was complete suppression of the causative organisms during the course of treatment in all instances; in five, however, recurrence of streptococci in the nose and throat was associated with the development of complications. Penicillin spray was found inefficient in ridding the nasopharynx of *Str. pyogenes*. These authors concluded that penicillin may have a beneficial clinical effect in low doses and still not eliminate

streptococci completely from the nose and throat. Large doses were thought to be relatively more active in this respect as well as in producing a lower incidence of complications.

Jersild[10] has reported the results of the treatment with penicillin of 1,000 cases of scarlet fever in Copenhagen. Intramuscular injection of 90,000 to 150,000 units of the antibiotic agent twice a day was found to rid the nose and throat of hemolytic streptococci within forty-eight hours. Therapy had to be continued for at least six days in order to prevent reappearance of the organisms in the pharynx. With this type of treatment, sore throats subsided rapidly, the average febrile period was only 4.5 days in contrast to 7 days in control subjects treated with sulfanilamide, and no complications developed. The rash was unaffected by penicillin.

The most recent investigation of the effect of penicillin treatment on streptococcal pharyngitis is that of Loge and Kilbourne.[14] Three groups were studied; one was treated "symptomatically," another received a single dose of 300,000 units of aqueous penicillin solution daily for six or seven days, and the third was given 20,000 to 50,000 units of the same drug intramuscularly every three hours for from four to seven days. Penicillin, whether administered continuously or intermittently, did not significantly modify the symptomatology of the pharyngitis but did reduce the period of pyrexia and leucocytic reaction. The infecting organisms were found to be eliminated rapidly from the pharynx, but early and frequent relapses were noted when therapy was discontinued after one to three days. Two of forty-seven patients who were treated with 300,000 units of penicillin once daily developed peritonsillar abscesses and elimination of streptococci from the pharynx in this group was less rapid than in those receiving more frequent injections. No late sequelae of streptococcal infection occurred in patients in whom effective blood concentration of drug had been continuously maintained for 47 days. Three cases of rheumatic fever followed treatment with 300,000 units per day. The incidence of positive cultures observed on the twenty-first day was greatly lessened whether penicillin was administered in daily or three-hourly injections.

The purpose of the work reported in this study was to make a detailed comparison of the effects of globulin and penicillin on the clinical course and laboratory findings in scarlet fever. This is the first of a series of reports concerning the results of the treatment of scarlet fever with penicillin in various dosages and administered by different routes at varying time intervals. Later papers will also concern themselves in more detail with blood levels of the antibiotic agent, with the development of nonsuppurative complications and alterations in immunity during the course of therapy.

METHODS

Three types of treatment were used in this study. Alternate admissions of patients with scarlet fever, regardless of their age or the severity of the disease, were given globulin (one dose intramuscularly), penicillin in a dose of 15,000 units intramuscularly every three hours for ten days, or only so-called "symptomatic" treatment consisting of bed rest, throat irrigations, etc., as soon as the

diagnosis was established. At the time of admission to the hospital, some attempt was made to grade the severity of the disease on the basis of the height of the fever, the extent and severity of the rash, the intensity of the pharyngitis, and the presence of such toxic manifestations as headache, nausea, vomiting, abdominal pain, and arthralgia.

Globulin was administered in doses of 20 to 60 c.c. depending on the size of the patient; no individual received more than 60 c.c. of this material and only one injection was given. The plasma derivative was injected intramuscularly, great care being taken not to introduce any of it intravenously. When large doses were employed half of the total quantity was put into each buttock. At times analgesics had to be given in order to alleviate the persistent pain resulting from the intramuscular deposition of this material. Five different lots of globulin having potencies of from 30 to 80 antierythrogenic units per cubic centimeter were used. Patients who had had scarlet fever for a period longer than forty-eight hours were not admitted to the study.

Throat and nose cultures were made at the time of admission and daily thereafter until discharge by means of sterile swabs which were streaked over blood-heart infusion-yeast-tryptose-agar. All temperatures were taken rectally every four hours. Complete physical examination was carried out daily. White blood counts were determined twice a week and the urine examined three times weekly during the entire period of residence in the hospital. Electrocardiograms were taken only in those instances where they appeared to be warranted. Changes in the appearance of the rash were followed carefully and time of its first desquamation noted. The pharynx of each patient was examined daily and the degree of lymphoid hyperplasia, redness, exudate if present, tonsillar enlargement, and difficulty in swallowing noted. The time of disappearance of such toxic manifestations as arthralgia, headache, nausea, vomiting, diarrhea, and sore throat were accurately determined. All patients were kept in the hospital for a minimum period of three weeks, while those who developed a complication or showed any abnormality in the course of their disease were detained for a longer period of time.

RESULTS

Two hundred and fifty-five patients with scarlet fever were included in this study; of these 102 received "symptomatic" therapy, 103 were given globulin, and 50 were treated with penicillin. Table I shows that, although the age range of the cases varied somewhat in the three groups, the average for each was approximately the same. This should tend to rule out any important variation in the course of the disease solely on the basis of age difference.

TABLE I. PATIENTS WITH SCARLET FEVER AND TYPES OF TREATMENTS

TREATMENT	NO. OF PATIENTS	MALE	FEMALE	AGE RANGE (YR.)	AVERAGE AGE (YR.)
Symptomatic	102	42	60	1-46	11.1
Globulin	103	58	45	2-57	11.5
Penicillin	50	27	23	2-35	11.1
Totals	255	127	128	---	---

The general mildness of scarlet fever in the past decade or more makes it rather difficult to classify this disease with respect to severity. However, an attempt was made to group the patients in this study with regard to the intensity of the clinical picture which was present at the time of admission to the hospital on the basis of the following criteria: *Severe:* temperature over 103° F., white blood count greater than 15,000, widespread rash with petechial and/or vesicular appearance, complaint of severe discomfort in the throat, marked edema, redness, exudate, and hyperplasia of the lymphoid tissue in the pharynx, and symptoms of severe toxicity such as headache, nausea, vomiting, and pains in the joints or muscles. *Moderate:* temperature between 101-103° F., white blood count from 10,000 to 15,000 per cubic millimeter, rash developing in typical order but not very bright and without petechiae, only moderate difficulty in swallowing, redness and edema of the pharynx but no exudate, and only slight or no symptoms suggestive of toxicity. *Mild:* temperature below 101° F., normal white count, rash quite sparse in distribution and light in color, discomfort in the pharynx minimal, redness of the pharyngeal mucous membrane only moderate without swelling or exudate; there were no signs of toxicity and in many instances the rash disappeared in about twenty-four hours. As can be seen from Table II, most of the persons in each treatment category were classified as having moderately severe infection. The distribution of severe and mild disease was also approximately equivalent, although the group receiving no specific therapy contained the smallest number of cases classified as mild. On the whole, however, in spite of complete chance alternate selection, the patients receiving the various forms of therapy were quite comparable as regards both age and severity of their scarlet fever.

TABLE II. SEVERITY OF SCARLET FEVER

TREATMENT	PER CENT OF PATIENTS		
	SEVERE	MODERATE	MILD
Symptomatic	33	55.3	11.7
Globulin	25.3	50.5	24.2
Pencillin	30	40	30

Serologic typing of the beta-hemolytic streptococci isolated from the nose and/or throat at the time of admission to the hospital was successful in 228 patients. The organisms were classified both as to group specific carbohydrate and M substance, the determinations being carried out using the Lancefield technique. All of the organisms studied were found to belong to Group A. No instances of pharyngitis due to other groups were observed in this study or in the ones to be described subsequently. As is illustrated in Table III, the commonest serologic types isolated during this investigation were 14, 18, 23, and 3. Seventeen other types were also demonstrated in the pharynges of various of the patients in this study. No correlation could be established between the serologic type of *Str. pyogenes* responsible for the initial infection and the severity of the disease, the response to treatment or the risk of development of suppurative and/or nonsuppurative complications.

TABLE III. SEROLOGICAL TYPES OF *Streptococcus pyogenes* ISOLATED FROM 228 PATIENTS WITH SCARLET FEVER

TYPE OF STREPTOCOCCI	NO. OF PATIENTS
14	28
18	23
23	22
3	22
10/12	18
5	17
17	16
29	14
31	14
22, 30, 26, 1	8 of each
28, 4, 33	4 of each
6, 13, 19, 32, 40	2 of each

The remarkably rapid defervescence in the early course of scarlet fever resulting from the administration of penicillin is illustrated in Table IV. The antibiotic agent produced return of temperature to normal about twice as speedily as either of the other therapeutic regimens. While practically all of the patients receiving penicillin had normal temperatures after four days, about 30 per cent of each of the other groups were still febrile beyond this time. Little difference in the rate of defervescence could be noted between those individuals given "symptomatic treatment" and those treated with globulin; as a matter of fact, the plasma derivative seemed to be least effective in reduction of fever in the first twenty-four hours of treatment. These findings may be interpreted as indicating a much more rapid eradication of the primary focus of infection in the pharynx by penicillin than was produced by either of the two other forms of management. This possibility is substantiated by the bacteriologic data presented hereafter and emphasizes the fact that in present day scarlet fever most of the fever is due to the local invasion by streptococci in the respiratory tract and not by the toxemia.

TABLE IV. EFFECT OF TREATMENT ON DECLINE OF TEMPERATURE IN FIRST FOUR DAYS

TREATMENT	PER CENT OF PATIENTS SHOWING RETURN OF TEMPERATURE TO NORMAL			
	1 DAY	2 DAYS	3 DAYS	4 DAYS
Symptomatic	24.5	37	48.02	70.5
Globulin	11.65	32	49.5	67.9
Penicillin	48.0	70.0	90.0	94.0

In each group of patients, a varying percentage of individuals suffered a secondary rise in temperature after defervescence had been established for a period of at least forty-eight hours. In the group treated symptomatically or with globulin no correlation could be established between the second episode of fever and recurrence of streptococci in the pharynx since the majority of these patients retained the organisms in their upper respiratory tract throughout the entire period of observation. In those given penicillin a return of streptococci in the nose and/or throat did not always accompany the febrile recrudescence. In several instances, however, a recurrent pharyngitis with or without a scarlatiniform eruption was present. In two patients rheumatic fever was suspected. The data relative to febrile recurrences are presented in Table V.

TABLE V. SECONDARY RISES IN FEVER DURING OR AFTER THERAPY

TREATMENT	NO. OF CASES	PER CENT
Symptomatic	22	21.56
Globulin	24	23.28
Penicillin	17	34.0

Marked differences were observed in the purely clinical responses to the various types of therapy. The group that fared most poorly from the standpoint of amelioration of signs and symptoms was the one which was given "symptomatic" treatment. These patients had persistence of the pharyngeal discomfort for a period averaging six days; no difference was discernible in the rate of relief of sore throat in those treated with gamma globulin and those receiving no specific therapy. Penicillin, however, produced rapid relief of pain in the pharynx, most cases having lost all discomfort in from one to three days. The rash persisted for approximately the same length of time in penicillin-treated as in untreated individuals (an average of 4.5 days). In those receiving gamma globulin, the rash faded very rapidly and in most instances had completely disappeared in from twenty-four to thirty-six hours after administration of the material. This result could have been anticipated in view of the large amounts of antierythrogenic antibody administered in the globulin. Other toxic symptoms such as nausea, vomiting, and generalized aching were also relieved very rapidly by the plasma derivative; relief of these symptoms was more rapid with penicillin than with "symptomatic" treatment, but the effect was not quite as rapid as that produced by gamma globulin.

TABLE VI. AVERAGE OF WHITE BLOOD COUNTS ON ADMISSION AND AFTER ONE WEEK OF TREATMENT. SECONDARY RISES DURING OR AFTER TREATMENT

TREATMENT	ADMISSION	TREATED FOR 1 WEEK	SECONDARY RISE IN WBC
Symptomatic	16,612	12,182	54.6%
Globulin	14,000	11,310	58.8%
Penicillin	15,080	9,840	32%

That penicillin was very effective in eradicating the primary focus of infection is borne out by the data (Table VI) relative to the rapidity of return to normal of the peripheral white blood count. As can be seen from the tabulated results the average white blood count at the time of admission to the hospital was approximately the same in all three groups. Within one week, however, it had returned to normal in those given penicillin but was still elevated in those receiving globulin or no specific therapy. The relationship between rate of return of the white blood count to normal and persistence of streptococcal infection is lent weight by the data presented in Table VII which show that most of the patients treated with penicillin were free of beta-hemolytic streptococci in the nose or throat within five days after initiation of treatment. Secondary increases in the number of peripheral white blood cells—those occurring after the count had been normal for at least three days—were almost twice as frequent in cases given gamma globulin or "symptomatic" treatment as in

TABLE VII. RELATION OF TYPE OF TREATMENT TO RATE OF DISAPPEARANCE OF *Streptococcus pyogenes* FROM PHARYNX

NO. OF DAYS AFTER ADMISSION TO HOSPITAL	PER CENT OF PATIENTS WITH NEGATIVE THROAT CULTURES TYPE OF TREATMENT		
	SYMPTOMATIC	GLOBULIN	PENICILLIN
1	0	1.94	44
2	1.96	3.98	68
3	1.96	5.82	84
4	7.84	5.82	92
5	7.84	11.64	96
10	9.80	23.28	96
15	29.40	27.16	
20	39.20	58.2	
21	51.00	36.08	
Cultures Negative on Admission and Never Positive	9.80	5.82	4

those injected with penicillin. In some of the antibiotic-treated individuals the rise in white blood cells could be correlated with a recurrence of pharyngitis due to *Str. pyogenes;* in others, rheumatic fever or sinusitis was suspected while in some no cause for the recurrent leucocytosis was discernible. In the other patients secondary bacterial or nonsuppurative complications were responsible, in most instances, for the elevated white blood count.

While it may be difficult to evaluate with great accuracy the results of treatment on such features as temperature, leucocytosis, rash, sore throat, and others, in as variable a self-limited disease as scarlet fever, the rate of disappearance of streptococci from the nasopharynx or other focus as a result of the application of a specific therapeutic regimen affords the most dependable measurement of the true effectiveness of therapy. Eradication of the organisms is most important since most of the suppurative complications of this infection probably depend on persistence of *Str. pyogenes* in the respiratory tract. Furthermore, from the public health standpoint, any form of treatment in scarlet fever is inadequate if it does not eliminate the causative bacteria from the primary focus completely so that the treated individual may return to his community without danger to others in his environment. The remarkable efficiency of penicillin and the relative inadequacy of the two other methods of management in this respect are well borne out by the data presented in Table VII. In the group given the antibiotic agent, 96 per cent of the patients no longer had demonstrable beta-hemolytic streptococci in their pharynx five days after first exhibition of the drug; the percentage free of organisms at the same time in the other groups was 7.84 for those receiving no therapy and 11.64 for those given globulin. The period of confinement in the hospital for practically all of the patients studied was twenty-one days, after which they were discharged to their homes and allowed to circulate freely in their communities. Table VII points out quite clearly the ineffectiveness of simple isolation or even treatment with gamma globulin in reducing effectively the dangerous streptococcus carrier state; about 51 per cent of those with symptomatic treatment and 36 per cent of those to whom globulin was administered were still harboring *Str. pyogenes* (Group A) in the nose and/or throat at the time of dismissal from the hospital. This is in marked contrast to the penicillin-treated group, all of

whom were free of streptococci when they returned home and therefore could not serve as a seed bed for the dissemination of infection.

In fourteen of the patients who were treated with penicillin during the early phase of scarlet fever and in whom the streptococci had been rapidly eradicated from the nose and throat, bacteriologic relapse occurred after cessation of therapy. In some instances the recurrence of the organisms could be correlated with a new episode of pharyngitis, fever, or leucocytosis, but in some only a single positive culture was obtained although daily examinations were carried out. The explanation for this finding was, at first, not clear but, as will be described in subsequent papers in this series, this phenomenon was found, in the main, to be due to the admission of patients with acute scarlet fever to the same wards in which individuals who had been freed of streptococci by penicillin treatment were residing. In some instances sudden appearance of streptococci in the nose and/or throat of a patient could be traced to a house-officer or nurse carrying the organisms. When patients were isolated on clean wards after five to six days of antibiotic therapy plus two negative throat cultures, and not allowed to mingle with fresh cases or personnel who were carriers, practically no instances of bacteriologic relapse were observed; when recurrence did take place on these "clean" isolation wards it could practically always be related to a nurse or house-officer who was a temporary carrier of *Str. pyogenes.* The data relative to the recurrences of streptococci in the nose and throats of penicillin-treated patients after cessation of therapy are presented in Table VIII.

TABLE VIII. RETURN OF STREPTOCOCCI TO PHARYNX AFTER CESSATION OF PENICILLIN TREATMENT

DAYS AFTER PENICILLIN THERAPY STOPPED	NO. OF PATIENTS SHOWING POSITIVE THROAT CULTURES
1	2
2	2
4	2
5	1
7	1
8	2
10	3
14	1

Further proof of the effectiveness of any agent used in the treatment of scarlet fever is adduced from its ability to reduce markedly or even eliminate completely the incidence of early or late suppurative and nonsuppurative complications. The detailed data regarding complications in the patients treated with the three regimens under investigation are presented in Table IX. Several differences in the groups are quite outstanding. First, is the lack of suppurative sequelae in cases treated with penicillin; the high incidence of recurrent sore throat is probably the result of improper isolation of these patients once they were freed of their streptococci. This matter has already been discussed. The relatively high rate of recurrent scarlet fever is probably the result of the action of two factors; one, the decrease in immune response to streptococcal infection following penicillin administration reported by Weinstein and

Tsao,[19] and the other, the matter of allowing these patients to come in contact with fresh cases of scarlet fever. Patients to be described in later reports on this subject showed no tendency to recurrence of streptococcal pharyngitis with or without a rash. No instance of proved rheumatic fever was found in those who received penicillin, but two cases were classified as suspects. This elimination of rheumatic fever by penicillin treatment of the acute phase of scarlet fever is probably more apparent than real and will be elaborated on in detail in another paper in this series.

TABLE IX. INCIDENCE OF COMPLICATIONS IN SCARLET FEVER PATIENTS TREATED BY VARIOUS METHODS

COMPLICATION	TYPE OF TREATMENT : PER CENT SHOWING COMPLICATIONS		
	SYMPTOMATIC	GLOBULIN	PENICILLIN
Proved rheumatic fever	3.82	2.91	0
Rheumatic fever suspect	1.96	2.91	4
Chorea	0.98	0	0
Mastoiditis (suppurative)	2.94	0.97	0
Suppurative otitis media	9.80	3.88	0
Catarrhal otitis media	0	3.88	0
Recurrent pharyngitis	3.82	1.94	18
Peritonsillar abscess	0	0.97	0
Recurrent scarlet fever	1.96	0	6
Glomerular nephritis	1.96	0	0
Purulent sinusitis	0.98	0.94	2
Cervical adenitis with fever	1.96	6.79	0
Pyodermia	2.94	0.97	2
Paronychia	2.94	0.97	0
Purulent conjunctivitis	0.98	0	0
Acute Str. osteomyelitis	0	0.97	0
Streptococcal pneumonia	0.98	0.97	0
Acute tracheitis	0.98	0.97	0

As might have been expected, gamma globulin exerted little if any effect on the development of suppurative or nonsuppurative complications. While the plasma derivative contains a large amount of antierythrogenic material it probably has little if any antibacterial activity; even if it did, the high degree of type specificity of streptococcal bacterial immunity would mitigate against its being effective in a group of patients in whom scarlet fever was produced by a wide diversity of types. Suppurative otitis media was found three times more often in the group given "symptomatic" treatment than in those receiving globulin. No explanation is at hand for this difference. Cervical adenitis with fever was present five times more commonly in individuals to whom the plasma factor was administered than in those who remained essentially untreated; this phenomenon is also without adequate explanation. On the whole, no profound effect of gamma globulin in reducing suppurative sequelae in scarlet fever could be discerned. As can be seen from Table IX, this material had no influence on the incidence of rheumatic fever; the difference between these results and those obtained by Landon and his co-workers, who reported a marked reduction in this nonsuppurative complication of scarlet fever following globulin administration early in the course of the acute infection, cannot be explained at the moment. The incidence of glomerular nephritis is usually low in scarlet fever (about 1 per cent) and the results obtained in this study are, therefore, probably

not very valid since the number of patients in each group was relatively small. Studies of much larger numbers of cases to be reported later will consider this point more carefully. It is interesting that, in the present series of patients, the only instances of acute glomerular nephritis occurred in the group receiving "symptomatic" treatment. While the impression may be created that both gamma globulin and penicillin given in the acute phase of streptococcal infection eliminate the risk of the subsequent development of acute hemorrhagic nephritis, this has not been borne out by later investigations. The entire problem of the occurrence of nonsuppurative sequelae in cases of streptococcal pharyngitis treated with penicillin will be discussed in detail in a later paper.

DISCUSSION

While scarlet fever is a disease in which all of the manifestations are the result of bacterial growth and invasion at some local site usually the pharynx plus the effects of widely disseminated toxins, the clinical picture as seen recently is rarely complicated by severe toxicity. In the main, the difficulties encountered in this infection are due to persistence or extension of the local focus or possibly the development of some form of hypersensitivity to the organism or its products. Effective treatment, therefore, should result in rapid sterilization of the primary site of invasion, speedy and complete eradication of the signs and symptoms of the acute disease, and the prevention of suppurative and nonsuppurative sequelae.

The group of patients given "symptomatic" treatment ran a more or less "typical" course; relatively slow recovery at the site of streptococcal invasion, very frequent persistence of the organisms for a period beyond the isolation time, and the development of local and distant bacterial and nonbacterial complications. This series of patients showed approximately the same incidence of the various sequelae as had been observed in large numbers of other cases in the years before this study was carried out.

Gamma globulin, as might have been expected because of its high content of antierythrogenic material, was found to produce very marked amelioration of the toxic signs and symptoms of scarlet fever with rapid fading of the rash and disappearance of such manifestations as headache, nausea, vomiting, and generalized muscle aching. Although some decrease in the incidence of suppurative otitis media was noted in the globulin-treated patients as contrasted to the controls, there was no remarkable reduction in the rate of occurrence of other suppurative complications following the administration of the plasma derivative. As a matter of fact, cervical adenitis with fever was found more commonly in those treated with gamma globulin than in those given no specific therapy. The effect of gamma globulin in reducing the incidence of rheumatic fever was not striking.

Penicillin appeared to be the agent of choice for the treatment of scarlet fever since it shortened markedly the course of the acute phase of the infection, eradicated the causative bacteria from the pharynx rapidly, prevented, for the most part, the development of suppurative complications, and allowed all patients to be returned to their communities free from beta-hemolytic streptococci

and, therefore, without danger to other individuals in their environment. The causes of the frequency of recurrent pharyngitis with or without a rash following penicillin administration could not be determined from the present study alone. Subsequent investigations of large groups of cases of scarlet fever treated with the antibiotic agent have not substantiated these findings. The return of streptococci to the pharynx with or without a recurrence of clinical disease following cessation of penicillin administration was probably completely due to contamination of treated individuals by fresh cases of streptococcal pharyngitis brought into the same ward or by contact with attendants who were temporary carriers of this organism. In many instances the bacteriologic relapse was very short-lived and did not result in a change in the course of the disease. While several patients given penicillin were considered to be rheumatic fever suspects, no frank instance of this complication was noted. The present study, however, does not present the true picture with respect to the incidence of rheumatic fever and glomerular nephritis following penicillin therapy of scarlet fever; these two sequelae will be discussed in complete detail in a later paper.

The patients discussed in this paper who received penicillin were given the crystalline G preparation every three hours intramuscularly, the dose being 120,000 units daily for ten days. Such a regimen of therapy imposes some hardship on both the patients and nursing personnel. While less frequent administration and possibly a more comfortable route for giving penicillin appear most desirable, only thorough investigation of these matters will yield the information necessary to change the regimen used in the present study so effectively. Rapid resolution of the acute phase of the disease and the eradication of serious complications must not be sacrificed merely for comfort and convenience in treatment. Time-dose relationships and influence of different routes of administration of penicillin in scarlet fever have been studied carefully and will be reported on in later papers in this series.

CONCLUSIONS

1. Two hundred and fifty-five patients with proved scarlet fever were treated by three different regimens, the cases for each type of therapy being chosen alternately.

2. Gamma globulin was found to cause very rapid fading of the rash but had no effect on the streptococci in the pharynx, allowed the carrier state to persist as long as it did in untreated patients and had little, if any, effect on the development of suppurative complications or such nonsuppurative sequelae as rheumatic fever.

3. Penicillin appeared to be the agent of choice in the treatment of scarlet fever because it caused rapid disappearance of the local focus of infection, eradicated *Str. pyogenes* from the pharynx speedily, eliminated the discharge of carriers from the hospital, and decreased markedly the incidence of the serious suppurative complications. The occurrence of rheumatic fever and glomerular nephritis following treatment of the initial streptococcal infection with penicillin will be discussed in a later paper.

REFERENCES

1. Ashley, P.: Treatment of Scarlet Fever, J. A. M. A. **130**: 771-774, 1946.
2. Cohen, E. J., Oncley, J. L., Strong, L. E., Hughes, W. L. Jr., and Armstrong, S. H. Jr.: The Characterization of the Protein Fractions of Human Plasma, J. Clin. Investigation **23**: 417-432, 1944.
3. Dingle, J. H., and Commission on Acute Respiratory Diseases: A Study of a Food-Borne Epidemic of Tonsillitis and Pharyngitis Due to B-Hemolytic Streptococcus, Type 5, Bull. Johns Hopkins Hosp. **77**: 143-210, 1945.
4. Epidemiology Unit No. 82, U. S. Naval Hospital: Observations on the Treatment of Scarlet Fever with Penicillin, Am. J. M. Sc. **211**: 417-420, 1946.
5. Fox, M. J., and Gordon, N. F.: Treatment of Scarlet Fever, Arch. Int. Med. **74**: 1-3, 1944.
6. Hirsh, H. L., Dowling, H. F., and Sweet, L. K.: Treatment of Various Infections with Penicillin X, With a Preliminary Note on the Value of Penicillin X in Scarlet Fever, Ann. Int. Med. **25**: 78-87, 1946.
7. Hirsh, H. L., Rotman-Kavka, G., Dowling, H. F., and Sweet, L. K.: Penicillin Therapy of Scarlet Fever, Comparison with Antitoxin and Symptomatic Therapy, J. A. M. A. **133**: 657-661, 1947.
8. Hoyne, A. L., and Brown, R. H.: Penicillin for Scarlet Fever, J. A. M. A. **133**: 661-663, 1947.
9. Jennings, R., and DeLamater, E. D.: Penicillin Therapy of Scarlet Fever and the Streptococcus Carrier, Am. J. Med. **2**: 1-22, 1947.
10. Jersild, T.: Penicillin Therapy in Scarlet Fever and Complicating Otitis, Lancet **1**: 671-673, 1948.
11. Kuttner, A. G., and Lenert, T. F.: Occurrence of Bacteriostatic Properties of Blood in Patients after Recovery from Streptococcal Pharyngitis, J. Clin. Investigation **23**: 151-161, 1944.
12. Landon, J. F., and Jackson, S. J.: Treatment of Scarlet Fever: A Comparison of Gamma Globulin with Other Agents in 1,667 Cases, Am. J. Dis. Child. **76**: 60-72, 1948.
13. Landon, J. F., and Greenfield, N.: Occurrence of Complications in Scarlet Fever Treated with Penicillin, Antitoxin, and Gamma Globulin, Am. J. Dis. Child. **76**: 380-383, 1948.
14. Loge, J. P., and Kilbourne, E. D.: Penicillin Treatment of Streptococcal Pharyngitis, Ann. Int. Med. **29**: 698-714, 1948.
15. Meads, M., Flipse, M. E., Barnes, M. W., and Finland, M.: Penicillin Treatment of Scarlet Fever, J. A. M. A. **129**: 785-789, 1945.
16. Plummer, N., Duerschner, D. R., Warren, H. D., Rogliano, F. T., and Sloan, R. A.: Penicillin Therapy in Hemolytic Streptococcic Pharyngitis and Tonsillitis, J. A. M. A. **127**: 369-374, 1945.
17. Rothbard, S.: Bacteriostatic Effect of Human Sera on Group A Streptococci, J. Exper. Med. **82**: 93-132, 1945.
18. Rubenstein, A. D., and Foley, G. E.: The Effect of Chemotherapy on the Duration of the Carrier State Following Scarlet Fever, New England J. Med. **233**: 315-322, 1945.
19. Weinstein, L., and Tsao, C. C. L.: In vitro Development of Temporary Penicillin Resistance in Streptococcus pyogenes, Proc. Soc. Exper. Biol. & Med. **66**: 598-602, 1947.
20. Wesselhoeft, C.: Sulfanilamide in Management of Acute Streptococcal, Particularly Scarlatinal, Infections of Upper Respiratory Tract, New England J. Med. **224**: 221-226, 1941.

AUREOMYCIN IN THE TREATMENT OF PERTUSSIS: A PRELIMINARY REPORT

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IN THE winter of 1948, clinical testing of aureomycin in the treatment of pertussis was begun at the United States Army Dependents Dispensary at Fort Hamilton, N. Y. At present, six patients manifesting severe forms of the illness have been treated. Because of the early recovery in these patients after aureomycin, despite a poor prognosis, a preliminary report of these cases is presented.

CLINICAL MATERIAL AND METHODS OF STUDY

Six patients with pertussis, diagnosed by history and observation of typical paroxysms, typical blood counts, exposure histories, and in two cases by positive nasopharyngeal cultures for *Hemophilus pertussis*, were selected for treatment. Four of these treated patients were considered critically ill prior to treatment.

Treatment with aureomycin* consisted of oral administration of material from capsules prepared for oral use, added to water or infant puréed fruits, every three to six hours. In general, doses of 350 mg. per kilogram of body weight per twenty-four hours were given for periods of 8 to 10 days with one exception as noted. These exceptionally high dosages were used because of the low toxicity and in an effort to obtain a definitive clinical result.

In three cases, hyperimmune serum was administered before the use of aureomycin and in one of these, streptomycin was given intramuscularly for an eighteen-hour period just preceding the start of aureomycin. In no case was other specific therapy given after start of aureomycin.

Clinical data concerning these cases is presented in Table I along with a summary of the results observed. In the table a distinction is made between the onset of the disease with coryza and fever and the first occurrence of paroxysmal coughing typical in this disease. As can be seen, three of these patients were critically ill on admission and two others were classed as having an illness that was "severe." The remaining patient, an older child, was only moderately ill.

RESULTS

Improvement in these patients after start of aureomycin was gradual and steady. Patients who were cyanotic and vomiting showed the greatest change and in general, by the third to fifth day these manifestations had cleared. Elevated temperatures, when present, subsided in this interval as well. Parox-

From the Pediatrics Service, United States Army Dependents Hospital, Fort Hamilton, N. Y.

*Obtained through the courtesy of Dr. Benjamin Carey, Medical Director, Lederle Laboratories, Division of American Cyanamid Company, Pearl River, N. Y.

TABLE I. SUMMARY OF SIX CASES RECEIVING AUREOMYCIN FOR PERTUSSIS

CASE NO.	AGE	PERIOD FROM INITIAL SYMPTOMS TO TREATMENT (DAYS)	PERIOD FROM ONSET OF PAROXYSMS TO TREATMENT (DAYS)	SEVERITY OF ILLNESS	AUREOMYCIN		DAY OF MARKED IMPROVEMENT AFTER START OF TREATMENT	CLINICAL IMPRESSION OF DRUG EFFECT
					MG./KG./DAY	NO. DAYS		
1*	12 mo.	14	10	Critical	365	9	9	Marked
2*	4 mo.	25	1	Critical	336	10	10	Marked
3	5 wk.	9	7	Critical	125	9	7	Marked
4	7 mo.	12	8	Severe	323	10	8	Moderate
5	14 mo.	27	8	Severe	374	8	8	Moderate
6	3 yr.	28	14	Moderate	100	10	10	Slight

*Nasopharyngeal culture positive for *Hemophilus pertussis.*

ysms of coughing persisted for a longer time, but with steadily diminishing frequency. All patients were virtually free of this symptom by the seventh to the tenth day after start of aureomycin and this is signified in the table as the period of illness after starting therapy. Convalescence after this initial period of improvement was uneventful. Brief descriptions of these cases follow.

CASE REPORTS

CASE 1.—This 12-month-old female infant was admitted to the hospital on the eighth day of illness. She was critically ill, required oxygen, and roentgenographic examination revealed complete consolidation in the left lung field. The total leucocyte count was 20,000 with 64 per cent lymphocytes. A nasopharyngeal culture yielded *H. pertussis.* During the first 6 hospital days she was treated with penicillin and sulfadiazine. In addition, she received during this time a total of 20 c.c. of hyperimmune pertussis serum. On the sixth hospital day only she received a total of 0.1 Gm. of streptomycin. At this time the patient continued to be critically ill, with massive consolidation of the whole left lung. She required oxygen constantly. Other therapy was discontinued and aureomycin in daily doses of 3 Gm. was started. Within 3 days oxygen was no longer necessary and the patient showed marked improvement. Improvement continued and by the finish of the 10 days of treatment, the child was eating well and had only occasional spells of coughing. Roentgenographic examination of lungs showed almost complete resolution of the consolidation. Convalescence was unremarkable.

CASE 2.—The result observed in this 4-month-old infant is considered the most remarkable among this group of patients. It is particularly striking because the age and severity of the infection made the prognosis in this case very poor.

On admission, history and physical examination suggested only a moderate bronchitis which had been present for about two weeks. The initial leucocyte count was 7,900 with 65 per cent lymphocytes. After 4 days' observation paroxysmal cough and whoop developed. At this time the leucocyte count was 42,000 with 58 per cent lymphocytes, and 2 days later a positive nasopharyngeal culture for *H. pertussis* was obtained. At this time the patient was observed to be critically ill. Cyanosis, vomiting and paroxysmal coughing became more severe and the patient was placed in an oxygen tent. As the only specific therapy, aureomycin was begun in daily doses of 336 mg. per kilogram of body weight and continued for 10 days. Definite improvement was noted by the third day when it was possible to discontinue oxygen therapy for long periods of time. Further improvement occurred and by the finish of therapy all whooping had ceased.

In this case the use of aureomycin was followed by the most marked toxic reaction of the series. Mild diarrhea with *severe* irritation of the whole buttocks area developed within 5 days after start of therapy. Also noted about the mouth, face, neck, and mouth where aureomycin was in contact, were severe areas of irritation which resembled first and second degree chemical burns. The mucosal surface of the mouth and throat also seemed to be irritated. At this time the drug was combined with small amounts of soda in solution at the time of administration. This mixture was then administered in fruit purée with better results. All irritated areas cleared 5 to 7 days after stopping the drug. It was also noted that the urine was colored a deep yellow during the period of drug therapy, presumably as a result of the aureomycin.

CASE 3.—A 5-week-old white female infant was admitted on the first day of paroxysmal cough with emesis, whoop, and cyanosis. Diagnosis was made on the basis of typical symptoms and blood count; the total leucocyte count was 28,900 with 71 per cent lymphocytes. Due to lack of drug at this time, hyperimmune serum was given on the second, third, and fifth hospital days. Despite this, the disease progressed in severity and aureomycin was administered. Treatment was started with 125 mg. per kilogram of body weight per day, given at six hourly intervals on the seventh day of the paroxysmal stage, ten days after the onset of the disease. Roentgenogram of the chest revealed evidence of pneumonia and cyanosis was marked, necessitating oxygen therapy. Within seven days, however, there was marked improvement with only a few mild coughing spells each day and complete absence of emesis and whooping. Recovery was uneventful and this infant was discharged for overseas travel on the twenty-first day of her illness.

CASE 4.—A 7-month-old white female infant was less dramatic in her recovery after treatment, but despite this a favorable course ensued with the use of aureomycin. On admission, the total leucocyte count was 19,000 with 78 per cent lymphocytes. Typical paroxysms, with whoop, emesis, and cyanosis were observed. The general well-being of the infant improved within 3 to 5 days after the start of treatment but the greatest evidence of improvement did not occur as shown in the chart until the eighth day. This case also showed the irritating effect of the drug, but was less marked when mixed with food and an alkaline solution at the time of administration of each dose.

CASE 5.—A 14-month-old female infant was admitted on the third day of the paroxysmal stage of the disease. The initial leucocyte count was 68,450 with 77 per cent lymphocytes and the infant had typical paroxysms with whoop and emesis and appeared acutely ill. Hyperimmune serum was given on the fourth and sixth days of paroxysms with no apparent effect. Aureomycin, 330 mg. per kilogram of body weight per day, given at three-hour intervals, was started on the eighth day of paroxysmal stage. After the start of aureomycin, the child developed chicken pox. After three days of therapy clinical improvement was noted with subsidence of whoop and emesis. There was no apparent effect of aureomycin on the course of the chicken pox.

CASE 6.—A 3-year-old child was admitted after a three weeks' illness at home and during a subsequent 6-day period of observation the diagnosis of pertussis was made by the observation of typical paroxysmal coughing and emesis. The total leucocyte count was 18,700 with 80 per cent lymphocytes. Aureomycin was started, 1.5 Gm. daily in divided doses, because of loss of weight, debilitation, and the prolonged course of the disease. After ninety-six hours of treatment, definite improvement of cough, whoop, and emesis was noted and during the next days of treatment the cough was no longer associated with emesis or whoop. Appetite improved and gain in weight was observed. By the finish of therapy the patient was greatly improved and free of symptoms.

COMMENT

This group of patients who received aureomycin represented, for most part, individuals in whom prompt recovery would not be anticipated. In fact, three of these patients were so ill that the outcome was in question. Despite this poor prognosis, almost complete recovery occurred in less than two weeks in all of these patients after the start of aureomycin. Although some of these patients received other therapy, the improvement in all occurred following the aureomycin alone. It would appear that the uniformity of the recovery following aureomycin, even whooping for periods ranging from 1 to 14 days before treatment was started, is the best evidence for drug-effect. Obviously, this small number of cases does not permit precise evaluation or adequate comparison with other types of therapy.

Because aureomycin has a wide spectrum of activity including gram-positive coccal organisms, and in some cases atypical pneumonia, as well as against gram-negative bacillary species, it is not possible to say that the favorable course observed in these patients could be the result of an effect solely on *H. pertussis* in these infections. Since the pneumonic involvement may well have been due to organisms other than *H. pertussis*, it is likely that these results may represent an effect against such organisms contributing to the infection.

It is of interest in the present study that these very large doses of aureomycin could be given for periods of more than one week with no serious toxicity occurring. Since recent experience has indicated that lower doses (100 mg. per kilogram per day) have been followed by prompt recovery in a variety of other aureomycin-susceptible infections in children, such a dose should be satisfactory for further study in the treatment of pertussis infections. Moreover, doses of this concentration have been accompanied by much less vomiting and local irritation than with those employed in this study. Since aureomycin can be given orally without risk of serious toxicity it would permit home therapy of many cases. For this reason it seems especially advisable to effect an evaluation of this drug in the treatment of pertussis. A study in this direction has been reported recently by Bell, Pittman, and Olson[1] who found that the period of whooping in twenty patients receiving aureomycin was appreciably shorter than that of a large group of patients not receiving this drug.

CONCLUSION

The rapid recovery of six patients with pertussis after aureomycin treatment suggests that this agent may be of benefit in this disease.

REFERENCE

1. Bell, J. A., Pittman, M., and Olson, B. J.: Pertussis and Aureomycin, Pub. Health Rep. 64: 589-598, 1949.

RESUSCITATION OF THE NEWBORN INFANT

Use of the Positive Pressure Oxygen-Air Lock

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AT THE present time there is much to be desired in the resuscitation of the asphyxiated newborn infant. Instrumentation, as the insertion of tracheal catheters or ventilation with air and oxygen, may lead to perforation. Bronchoscopic examination and aspiration affords complete relief only from six to eight hours after instrumentation. Mouth-to-mouth breathing is not only strenuous but carries a risk of infection to the infant.

Best and Taylor[1] state that the methods of resuscitation effective in the adult are likely to fail in the infant. The basis for this failure rests in the collapsed alveoli of the atelectatic lung that have failed to expand.

A new method and means of resuscitation and oxygenation of the asphyxiated newborn infant has been used under my direction at the St. Joseph's Maternity Hospital in Houston, Texas, since Jan. 4, 1950. The theory upon which the method is based is that resuscitation of the asphyxiated newborn infant is managed best by continuing in as far as possible the mechanics of labor. It is my belief that labor serves a twofold purpose. The obvious purpose is the delivery of the infant. The second purpose, and I believe as important as the first purpose, is the conditioning of the infant to promptly initiate his respirations.[2]

Briefly, the mechanism of my method in following that of labor is to provide the infant with heat, humidity, lack of handling, and oxygen and carbon dioxide pressure gradients for the favorable handling of those gases. In addition the expansion of gases is utilized for the expression of fluids and secretions in the pulmonary tree. A full report will be made later on this phase of the resuscitation of the asphyxiated newborn infant.

A satisfactory method of total oxygenation for the newborn asphyxiated infant has been found to occur when the infant is placed in a positive pressure oxygen-air lock and the pressure cycled between 1 and 3 pounds at one-minute intervals.

The means for employing total positive pressure and cycling those pressures in a manner similar to labor is an air lock designed to contain the asphyxiated infant as soon as signs of asphyxia appear.

The original positive pressure oxygen-air lock suitable for the resuscitation of the asphyxiated newborn infant is shown in Figs. 1, 2, and 3. A later model manufactured* for use in the various hospitals in Houston is shown in Fig. 4.

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*Manufactured by The Loewenstern Corporation, Houston, Texas.

Fig. 1.

Fig. 2.

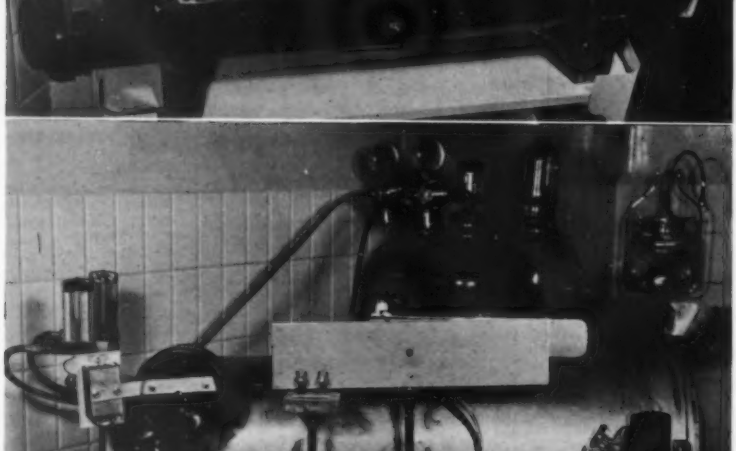

Fig. 3.

The body of the original air lock was made by sawing an ordinary aluminum pressure cooker in half and welding in a center body of sheet aluminum, making the over-all length of 37 inches with a diameter of 12 inches.

A heating and humidifying unit was placed in the closed end. Two flowmeters, one for air and one for oxygen, were placed also in the closed end above the heating and humidifying unit.

A plastic viewing window was constructed in order to observe the infant in the lock. A light above the window was added for adequate observation.

Metal contact points were placed in the air flowmeter in order to light a danger light and sound a warning buzzer when the rate of inflow of air ever reached a predetermined minimum rate. A safety escape valve was designed to limit pressures to 3½ pounds per square inch in the air lock.

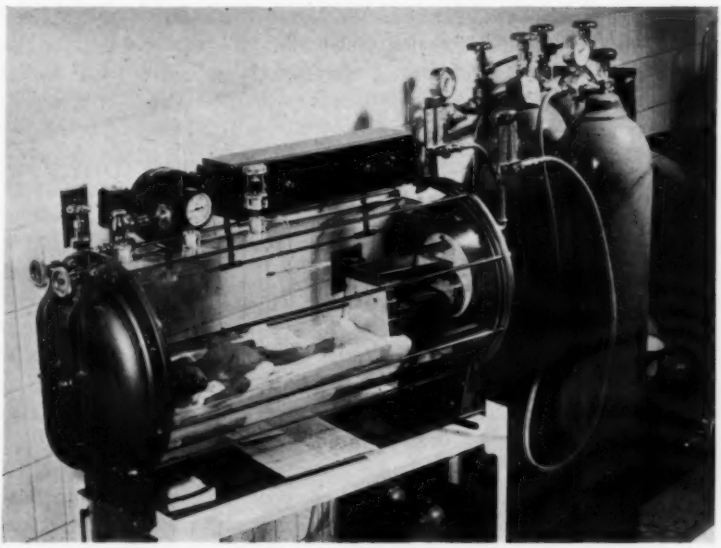

Fig. 4.

A pressure gauge was placed on the back to indicate pressures between 0 and 5 pounds per square inch.

In order to cycle the pressures automatically a Mercoid pressure switch working in conjunction with a motor valve was attached to the back of the machine. The Mercoid switch was set to open the motor valve at 3 pounds pressure and close it at 1 pound per square inch of pressure.

A hand valve was attached to the motor valve in order to regulate the rate of drop in pressure.

A hand exhaust valve was attached to the removable cover in order to maintain a steady pressure when the Mercoid switch was turned off.

Figure 3 shows the back of the pressure air lock and the attaching of the Mercoid pressure switch, safety valve, pressure guage, and motor valve with hand valve.

The advantages of positive pressures in the resuscitation of the asphyxiated newborn infant at this time appear to be:

1. The promotion of bronchial drainage.
2. A more uniform alveolar aeration.
3. Increase of any absorption of oxygen through the skin.
4. Relieving and protecting against atelectasis.
5. Provides a breathing exercise and improves muscle tone.
6. Combats acute pulmonary edema.
7. Provides favorable conditions for the diffusion and use of oxygen by the premature infant.

The lock operates in the following manner. First: The lock is maintained in a heated and humidified condition in the delivery room in order to provide without any loss of time essentially the same conditions as the environment from which the infant has been delivered. Second: The infant is placed under a pressure of 2 pounds, which is cycled to 3 pounds for a pound greater pressure for the positive phase of the breathing exercise. It is then reduced to 1 pound which provides a negative pound of pressure for the negative phase of the breathing exercise. These pressures are in line with those employed in labor by the infant's mother in the second stage of labor.

The timing of the positive and negative phases of the breathing exercises are 30 to 40 seconds for the positive phase which increases the pressure from one to three pounds, and fifteen seconds for the negative phase which decreases the pressure from 3 to 1 pound. Originally a shorter period was used for the reducing of the pressure from 3 to 1 pound, but some infants appeared to have a little difficulty in breathing across the negative phase when it was shorter than fifteen seconds. The expelling of fluids seemed to be effective at a fifteen-second rate of reduction of pressure so this rate was arbitrarily taken. Theoretically a greater expansion of pulmonary gases will be obtained on a quick release of pressure and carbon dioxide and fluids will be expelled more rapidly.

When oxygenation is effected and regular respirations established, a steady pressure of 2 pounds is employed with 60 per cent oxygen to continue adequate oxygenation. This pressure is reduced at intervals, observing carefully the infant, and if any cyanosis of the feet or hands occurs, the cycling is started at once. Again attention is called to the rate of cycling which is sufficiently slow and conforms to a pattern that the infant apparently can breathe across either the positive or negative phase with no difficulty.

The alternating positive and negative pressures and the maintaining of a positive pressure of 2 pounds of 60 per cent oxygen in this air lock oxygenates the asphyxiated infant in the following manner:

(1) There is an initial expelling of any fluid in the respiratory tree by positive pressures created by the expanding gases. This is seen in a number of infants, approximately one out of every five, by the outpouring of fluid and secretions from the mouth and nostrils. Fluids may be expressed immediately from the pulmonary tree after the infant has been placed in the lock, or may occur after some minutes. It may well be that the initial rate of decrease of pressure be lowered to five to ten seconds if the infant does not immediately expel fluids in order to expedite the freeing of the respiratory tree. If no

fluids or secretions are expelled by the increased rate of expansion of gases in the respiratory tree within five minutes, it is likely that none are present and the rate of decrease in pressure from 3 to 1 pound be set at fifteen seconds. This phase of resuscitation by the positive pressure air lock will be dealt with in detail in a later report.

(2) There is a gentle compression of the thoracic cage by means of the resistance of the bronchial tree to the pressure wave of gases diffusing into the alveolae and the pulmonary sacs when the pressure is being raised in the lock. This pressure wave is but momentarily delayed by the bronchial tree and according to Barach[3] effects a differential of not more than 5 cm. of water. However, this differential is operative in the Bloxsom Air Lock over a positive phase from atmospheric to 3 pounds pressure initially and from 1 to 3 pounds after the lock has been operating. The differential is operating also for the diffusion of carbon dioxide during the negative phase from 3 to 1 pound. At no time though is the total differential on the pulmonary tree more than 5 cm. of water thus making it impossible to develop pulmonary signs or symptoms of trauma.

The flow of gas through a duct system is influenced by:

a. The effective pressure differential (the diffusion gradient) between the ends of the duct. Ordinarily it is about 50 mm. Hg for the adult in normal health.
b. The cross section area of the duct.
c. The length of the duct.
d. The character of the walls of the duct.
e. The velocity of the gas.
f. The obstructions or restrictions in the duct.

(3) There is a gentle expansion of the thoracic cage by means of the resistance of the bronchial tree to gases diffusing out of the alveolae and pulmonary sacs when pressure in the lock is lowered from 3 to 1 pound. This negative pressure differential between the infant's blood and air leaving the pulmonary alveoli and sacs is conducive to establishing a diffusion gradient for carbon dioxide to be effectively expressed from the blood.

From Jan. 4, 1950, when the positive pressure oxygen air lock was first used, until March 26, 1950, the time this report was formulated, a total of 55 infants out of 1,372 infants delivered have been processed in this lock at the St. Joseph's Maternity Hospital in an attempt to habituate them to extrauterine conditions. This is a percentage of 4 per cent. No infant has lived less than ninety minutes in the lock and out of eleven deaths, five lived twenty-four hours, and two ten hours or longer before death. Table I shows the number of infants who have been through the lock.

Post-mortem examinations have been made on three of the eleven infants who died in the lock. Two of the infants had difficult breech deliveries and

TABLE I

		LIVING	DEAD
Number of infants resuscitated in lock	55	44	11
Premature infants	24	15	9
Term infants	31	29	2
The lock used in resuscitation of 4 infants in every 100 deliveries			

showed tentorial tears and intracranial hemorrhages. The third infant had erythroblastosis fetalis. The air lock is an efficient oxygenator, but so far in the majority of cases has been used as an instrument of last resort. From the statistics available, I believe that fortunately it will make no difference in the mortality rates of infants whose survival might be accompanied with an unusually high degree of cerebral injury.

A later report will be made on three of the premature infants who required positive pressure for periods of four to ten days in the lock. The increased diffusion and use of oxygen in those infants was made possible by the increased pressure of the lock.

The advantages of positive pressures used in an oxygen air lock for the resuscitation and oxygenation of the asphyxiated newborn infant are two, the immediate and the future. The immediate advantage to the infant is shown in Table II.

TABLE II. DEATH RATES OF INFANTS AT THE ST. JOSEPH'S MATERNITY HOSPITAL

	JAN. 1, 1949 TO JAN. 1, 1950	JAN. 1, 1950 TO MARCH 24, 1950
Infants delivered	6,324	1,372
Deaths of all infants	123	20
Death rate	1.94%	1.45%

The drop in the death rate from 1.94 per cent to 1.45 per cent represents a 25 per cent decrease in the St. Joseph's Maternity Hospital. In all fairness it must be stated that there has been a slight decrease in the incidence of premature infants which would lower the death rate some, but the incidence of the decrease in the number of premature infants has not been enough to account for the decrease in the death rate.

Henderson[4] states that the first quarter of an hour after birth is the most dangerous period of life. Eastman[5] insists there is only urgent indication in the treatment of asphyxia neonatorum, and that is the introduction of oxygen into the circulating blood of the infant. Cole[6] reports that the normal infant takes his initial gasp within two seconds after birth, cries by five seconds, and regular respirations become established within ten seconds. A delay of 30 seconds is abnormal and is an urgent indication that some inhibitory respiratory factor is operating. The immediate advantage of adequate and prompt oxygenation of the asphyxiated infant is that he will live.

The future advantages of adequate and prompt oxygenation of asphyxiated infants appear in later life in missing harmful central nervous system changes caused by anoxia. It is impossible at this time to evaluate the long term advantages to the asphyxiated infant by prompt oxygenation by the air lock in the elimination of central nervous system changes caused by anoxia immediately following birth. Schreiber, Kimball, and Whitley, quoted by Cole,[6] found in a study of asphyxia at birth in a group of Detroit school children that the backward and subnormal group gave a history of anoxia at birth four times the incidence of anoxia in their siblings and normal children in the same community.

Cole[6] believes that the relationship between asphyxia at birth and serious degenerative changes in the central nervous system is definitely established. Until infants who graduate from the positive pressure air lock are allowed time to develop and enter school, it will be impossible to adequately evaluate the long-term advantages of this machine.

A detailed study on the use of the tracheal catheter in asphyxiated infants will be the subject of a later paper. At this time it is possible to state that the resuscitating physician cannot possibly judge the infant whom it might be theoretically used on. Further, if rupture of the lung or stomach does not occur from its overzealous use, the mortality rate in the group of infants the catheter was used on is almost twice that of the group it was not used on. The danger of the tracheal catheter cannot be too vigorously emphasized at this time.

Wiping the throat with gauze on a finger and suctioning with a soft rubber ear syringe also must be reviewed. Frequently hemorrhages into the soft palate are seen. The carrying in of bacteria and monilia from the outside of the mouth to the inside and throat with subsequent possibilities of infection must be considered. Frequently, poor nursing on the part of the infant due to trauma of the throat may be seen during the first few days of life and is tremendously disturbing to the mother trying for the first time to nurse her infant. The most that can be said for this means of resuscitating the asphyxiated infant is that it is the least harmful.

The use of the positive pressure oxygen air lock is indicated in any situation requiring oxygenation of the full-term infant or premature infant. A few clinical conditions are given in Table III.

TABLE III. INDICATIONS AND COUNTERINDICATIONS FOR USE OF PRESSURE LOCK

A. Indications:
1. Cesarean section. At the present time it is believed that processing of infants delivered by this method for a period of at least 15 hours will be of great value.
2. Prematurity. Approximately one out of every eight premature infants have had to remain in the pressure lock from four to ten days.
3. Shock. The pale, cold, slightly cyanotic, slow breathing infant with a slow pulse is helped tremendously by positive pressure processing.
4. Cerebral edema manifested by grunting and slight cyanosis.
5. Atelectasis is best treated by cycling positive pressures when the infant is in the lock.
6. Pulmonary edema manifested by râles and outpouring of fluids from the respiratory tree is ideally treated by positive pressures for the expelling of that fluid.
7. Anesthetized infants are oxygenated, humidified, and kept warm in the air lock.
8. Narcotized infants are oxygenated, humidified, and kept warm in the air lock.
B. Counterindications:
1. Pneumothorax. The mechanics of the air lock will only serve to make a pneumothorax worse.

The practical use of the positive pressure oxygen air lock is as follows: The lock is kept heated at 100° F. at all times in the delivery room. Before the infant is placed in the lock, air is turned on at the flowmeter for air and allowed to run in at 8 liters per minute. Oxygen is started through the oxygen flowmeter at 8 liters per minute and this provides an oxygen concentration in the lock of 60 per cent.

The infant is placed gently in the lock, preferably not later than 30 seconds after failure to breathe or breathe properly. No clothing or covering is placed

on the infant and all suctioning by bulb syringe or tracheal catheter is to be omitted. The infant is kept in a horizontal position in order not to increase any cerebral edema. Practically it has been found that fluids will be expelled from the infant's nose and mouth when he is in this position.

The cover of the air lock is closed, locked, and the warning and automatic switches turned on for proper functioning of the lock to initiate respirations.

As the pressure rises to 3 pounds per square inch, one can observe if there are any pulmonary fluids or secretions in the pharynx by a flowing out through the mouth and nose of a frothy fluid. At the same time the infant begins to absorb oxygen through his skin and upper-respiratory tree with a beginning improvement in his color. At times the infant becomes quite red and it is believed that the extrapulmonary absorption of oxygen constitutes a very important step in the initial oxygenation of the infant. Frequently, as the pressure is released initially, the first respiratory gasp is made. With the initial pressure rise and cycling started the infant becomes well oxygenated and regular respirations become established in a short time in the majority of infants.

The cycling is continued until the respirations are regular. Then the pressure is maintained at 2 pounds per square inch for several hours or more. After a period of regular breathing and adequate oxygenation at 2 pounds of pressure, the pressure is reduced to 1 pound, and if no cyanosis appears on the feet or hands the lock is opened. At the end of this time the infant is placed in a standard incubator under 60 per cent oxygen and if his color continues satisfactory, he is transferred to a nursery and continued under oxygen until ordered discontinued by his physician.

At this time it appears from three of our permature infants who have been processed in this lock that an increased air pressure will play an important part in the life of approximately 12 per cent of the asphyxiated premature infants. These infants when removed from the lock in the periods of four to ten days showed great respiratory embarrassment when placed in the standard incubators under oxygen concentrations of 60 per cent and had to be re-entered into the pressure lock. Wilson, Long, and Howard,[7] in 1942, reported that a majority of premature infants they studied showed a certain rhythmic type of respiration when breathing air, but which assumed the normal adult pattern on the administration of additional oxygen. In a recent further study by Graham, Reardon, and Wilson,[8] of the oxygen saturations of the bloods of premature infants breathing air and then air enriched with oxygen, they came to the conclusion that there is an under-pulmonary ventilation in those infants. In the positive pressure air lock 60 per cent oxygen under 2 pounds of pressure either increases the diffusion rate of oxygen in the plasma of the infant, enables the fetal tissue cells to utilize oxygen more readily, increases the absorption of oxygen extrapulmonary, or forces the fetal hemoglobin to give up oxygen more readily. A certain number of premature infants will require more than atmospheric pressure for proper oxygenation. This observation in full will form the basis of a future report.

SUMMARY

1. Infants may be oxygenated quickly and respirations stimulated under an increase of total oxygen and carbon dioxide diffusion pressures.

2. The absorption of oxygen through the skin and upper-respiratory tract is a most important mechanism for the initial onset of respiration. Varying of pressure aids in this mechanism.

3. Oxygen appears at this time to be the one gas necessary for the prompt stimulation of the respiratory center.

4. The diffusion of oxygen in the plasma and its use by the tissue cells of the premature infant is favored by pressure in a considerable number of premature infants. In 12 per cent of the premature infants processed by positive pressure it appears that positive pressure is the only mechanism enabling the premature infant to get by the respiratory block seen developing early in life.

5. The expansion of gases expels fluids and secretions from the upper-respiratory tract in approximately one of five asphyxiated newborn infants.

6. Total positive pressures employed by the mother in labor and used in this study subjects the infant to no danger and may be continued for long periods.

7. The placing of an infant in a positive pressure oxygen air lock for resuscitation eliminates the possibility of danger from perforation of the lungs and intestines seen in a few attempts with vigorous manual resuscitation.

8. The tracheal catheter from this study and other studies indicates that it is an instrument fraught with danger and its use should be discontinued.

9. The mortality rate in a large maternity hospital has been lowered approximately 25 per cent from a slight reduction in the premature delivery rate and the use of the positive pressure oxygen air lock in resuscitating asphyxiated newborn infants.

I wish to thank the Obstetrical Staff of the St. Joseph's Maternity Hospital and Sister Carmen in charge of the delivery rooms for their invaluable aid in making this study possible.

REFERENCES

1. Best, Charles Herbert, and Taylor, Norman Burke: The Physiological Basis of Medical Practice, ed. 5, Baltimore, 1950, Williams & Wilkins Company, p. 358.
2. Bloxsom, Allan: The Difficulty in Beginning Respiration Seen in Infants Delivered by Cesarean Section, J. PEDIAT. 20: 215-222, 1942.
3. Barach, Alvan L.: Continuous Immobilization of the Lungs by Residence in the Equalizing Pressure Chamber in the Treatment of Pulmonary Tuberculosis, Dis. Chest 12: 3, 1946.
4. Henderson, Yandell: The Prevention and Treatment of Asphyxia in the Newborn, J. A. M. A. 90: 583, 1928.
5. Eastman, Nicholson J.: Foetal Blood Studies, III. The Chemical Nature of Asphyxia Neonatorum and Its Bearing on Certain Practical Problems, Bulletin of the Johns Hopkins Hospital, 50: 39, 1932.
6. Cole, W. C. C.: Asphyxia During Delivery and Immediately Post Partum (Round Table), J. PEDIAT. 19: 263, 1941.
7. Wilson, James L., Long, Susan Brochett, and Howard, Phillip J.: Respiration of Premature Infants, Am. J. Dis. Child. 63: 1080, 1942.
8. Graham, Bruce D., Reardon, Helen S., Wilson, James L., Tsao, M. U., and Baumann, Mary L.: Physiologic and Chemical Response of Premature Infants to Oxygen-Enriched Atmosphere (Society Transactions), Am. J. Dis. Child. 79: 371, 1950.

INCOMPLETE PANCREATIC DEFICIENCY IN CYSTIC FIBROSIS OF THE PANCREAS

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TESTS of pancreatic exocrine function form the basis of the laboratory means of diagnosis of cystic fibrosis of the pancreas during life. The deficiency of pancreatic enzymes in the typical case is indeed striking. The literature, however, contains items of evidence that the pancreatic lesion is not always complete.

Sinclair has reported an autopsy diagnosis of a 5-month-old infant with cystic fibrosis of the pancreas in whom only approximately one-half of the pancreas, and that mostly in the tail, appeared to be involved.[1] This infant had had a normal concentration of trypsin in the duodenal aspirate and a normal output of stool fat. The usual bronchitis and bronchopneumonia had led to death.

Reports of two patients dying at the age of 17 years have appeared within the past two years.[2, 3] In another report a 35-year-old Negro man was considered to have died of cystic fibrosis of the pancreas manifested by bronchopneumonia, a fatty liver, and a cystic and fibrous pancreas.[4] It is difficult to be sure that the disease in this case was really of the same etiology as the typical fibrocystic disease of the child. A similar picture could presumably result from pancreatic obstruction of other etiology followed by a poor nutritional state favoring pneumonia.

Great variation in the involvement of various organs occurs. In some instances there is little or no clinical evidence of pulmonary involvement for many years. In some, notably older children, the hepatic involvement becomes prominent[5, 6, 7] and may in fact be the development leading to death. Marked involvement of the salivary glands and other organs is seen in some cases but not in others. If the disease should be a widespread biochemical error, a similar variability of the pancreatic defect might also be expected to occur.

Andersen,[7] in a re-examination of the routine autopsies of 1,000 infants and children, studied microscopic sections of the pancreas of 605 and found 20 cases, each of which was estimated to have over 90 per cent involvement of the pancreas. Another 21 cases had from 20 to 90 per cent involvement. In the latter group only 3 had the clinical picture of cystic fibrosis of the pancreas. There is thus pathologic evidence of a group of subclinical cases approximately as large as the group of cases clinically manifest by the usual signs and symptoms of cystic fibrosis of the pancreas.

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Certain characteristics of the pathologic changes of the pancreas have been noted to be progressive in autopsies of different ages.[7, 8] Perhaps a counterpart of this finding is the presence of trypsin in the stool by the x-ray film test in 7 out of 29 infants with cystic fibrosis of the pancreas.[9]

The present report is occasioned by two cases of cystic fibrosis of the pancreas proved by autopsy. In one case, J. F., normal vitamin A absorption curves occurred. In the other, Case J. N., the trypsin concentration of the duodenal drainage was in the normal range at the age of 8½ months.

CASE REPORTS

CASE J. F.*—This infant was first seen at San Francisco Children's Hospital at the age of 10 months with history of cough for six months followed by dyspnea and cyanosis. He had had radiation to the thymus, penicillin, celiac diet, and various other treatment. He weighed 6.1 kilograms and had the cough, sputum (swallowed), crackling râles, clubbing, and emaciation characteristic of the syndrome of cystic fibrosis of the pancreas, but had less than the usual abdominal protuberance. Little or no fat was seen in the stool in repeated microscopic examinations with sudan III.

Duodenal drainage was done with an infant-size bilumen gastroduodenal tube and the trypsin concentration was 1.8 as compared to a normal range of 26 to 149 by the modified Anson method.[10] Amylase and lipase were low, but present to a comparable degree. The trypsin value of 1.8 was relatively high in the range of cases of cystic fibrosis of the pancreas in the present series of studies, 32 of the 38 cases (Table I) having values of 0.8 or less.

TABLE I. TRYPSIN CONCENTRATIONS IN DUODENAL DRAINAGE, AND RISES OF PLASMA VITAMIN A IN ABSORPTION TESTS

	TRYPSIN*				RISE IN VITAMIN A†			
Case J.F. Age 10 months	1.8				137, 161			
Case J.N. Age 8½ months	46				36			
Age 14 months	1.4							
	MEAN	SD‡	MAX.	MIN.	MEAN	SD	MAX.	MIN.
32 cases of cystic fibrosis of the pancreas with "typical" trypsin concentrations	0.11	0.16	0.8	0	5.1	10	39	−7
4 cases (ages 5 months to 4 years) of cystic fibrosis of the pancreas with trypsin concentrations slightly above the "typical" range (not including Cases J.F. or J.N.)	3.3	--	5.5	1.2	20	--	89	−8
Normal subjects: Trypsin in 18 cases, vitamin A in 15	80	34	149	26	219	97	407	67

*Approximate Anson units × 10^4 per milliliter, duodenal drainage by bilumen gastroduodenal tube without secretin.

†Micrograms per 100 ml., maximum rise from fasting to three- or five-hour level with dosage of 7,000 I.U. vitamin A per kilogram as halibut liver oil.

‡SD = standard deviation.

Vitamin A absorption tests were done without pancreatin. The fasting value was 33 μ per 100 c.c. and the three- and five-hour values rose to 122 and 170 respectively. The test was repeated two days later and again showed a rise, the fasting value being 46 and the three- and five-hour values 58 and 207. In fifteen normal subjects the average curve has been found to start at 46 ± 20,† and

*The authors are indebted to Dr. E. B. Shaw for the privilege of studying and reporting this patient.

†Standard deviation.

rise to 234 ± 102, and 231 ± 84 in three and five hours. In spite of treatment with oxygen, penicillin (aerosol and intramuscular), pancreatin, vitamins, and other drugs, the patient continued to fail and died at the age of 22 months.

The pertinent findings of the organs at autopsy were limited grossly to the lungs and pancreas and provided a definite diagnosis of cystic fibrosis of the pancreas. The lungs were pale with hyperdistention and showed a certain degree of mottling. Upon sectioning the abnormality immediately noted was much thick inspissated material in the bronchi. The bronchi seemed to be dilated and ectatic. There was some slight surrounding congestion and minimal pneumonitis. The *pancreas* was approximately one-half the normal size. It had lost its lobular pattern and upon sectioning was firm, quite fibrous, and generally atrophic. The pancreatic duct was not identified with certainty in the fibrosed organ.

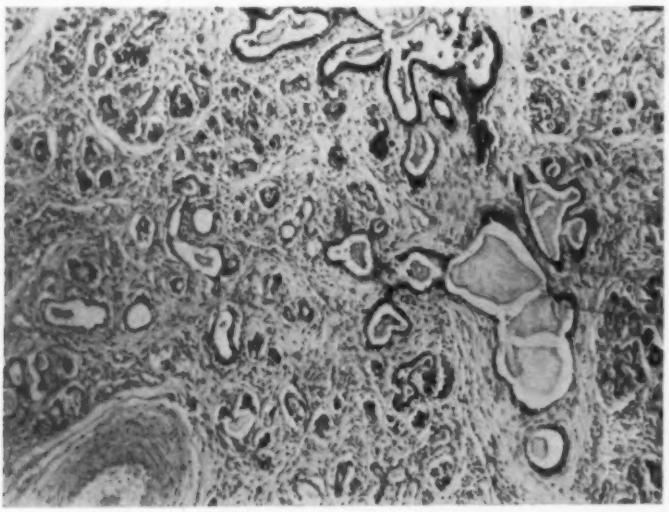

Fig. 1 (J. F.).—Marked ductal and acinar ectasia is evident with advanced fibrosis and parenchymatous atrophy. (×100.)

Microscopically, in the lungs, the major area of reaction is bronchial where there is noted frank ulceration of the epithelium which is even occasionally metaplastic. There is much surrounding fibrosis and destruction of the bronchial wall. There is little inflammation in the alveoli proper. In the pancreas (Fig. 1), the extent of fibrosis is marked with associated chronic inflammatory cells of a nonspecific variety. The ducts are frequently dilated, lined by a low epithelium, and sometimes contain some apparently thick secretions. The glandular elements are markedly decreased in number and poorly developed. They show only abnormal acinar formation and practically no zymogen granules in the cells. Islet tissues are identifiable, but also distorted by the fibrotic process. On an average the exocrine elements are approximately 70 per cent destroyed in this process.

CASE J. N.—This infant was first seen at the University of California Hospital at the age of 8½ months. There was history of increasing cough and sputum since the newborn period. Some history of large foul stools was elicited

but constipation was the more common complaint. There was a questionable degree of abdominal protuberance. The buttocks were flat and severe emaciation was general. Weight was 4.2 kilograms. No râles were heard at that time. A vitamin A curve with pancreatin showed a high normal result (fasting 52, three-hour 458, five-hour, 250). Without pancreatin, the rise was less but still greater than in the usual case of pancreatic deficiency. The curve in this patient was fasting 34, three-hour 70, five-hour 47, whereas in cystic fibrosis of the pancreas it has been fasting 34 ± 12, three hour 37 ± 15, five-hour 36 ± 15 in the average of thirty-two cases with typical duodenal drainage findings.

Duodenal drainage with the bilumen tube, but without secretin, gave a scanty juice with a trypsin concentration of 46 μg as compared to normal values ranging from 26 to 149 and typical fibrocystic values ranging from 0 to 0.8.

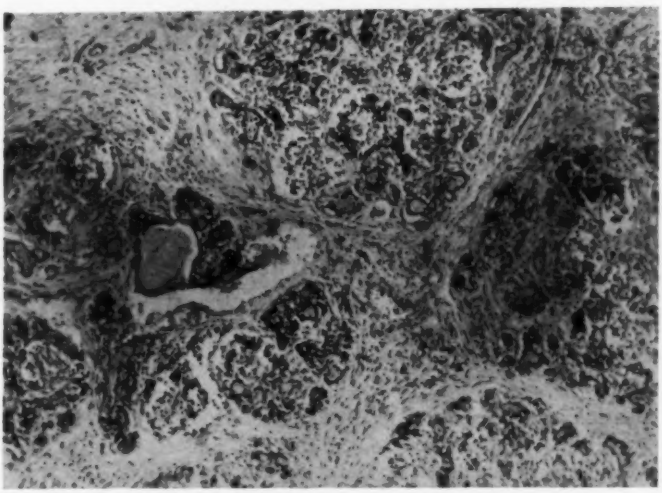

Fig. 2 (J. N.)—The lobular architecture is discernible, but extensive fibrosis is evident. The acini are present but dilated and lined with a low atrophic epithelium. (×100.)

After six months with little treatment other than occasional penicillin injections, the infant weighed 4.2 kilograms. Her lungs were full of coarse râles and her sputum flora was 95 per cent *Pseudomonas aeruginosa* not sensitive to 50 units per milliliter of penicillin, and 5 per cent *Staphylococcus albus* inhibited by 15 units of penicillin. Her white blood cell count was 21,400 and she was febrile and dehydrated. Her chest x-ray showed emphysema, fibrosis, and inflammation. When she became afebrile, duodenal drainage was again done with the bilumen tube and this time secretin was used. Prior to secretin injection, the somewhat scanty flow was 1.1 ml. in twenty minutes. After secretin the volume was 0.9. A volume flow approximating 4 to 8 ml. after secretin would have been considered normal. Trypsin concentration was 1.4 before secretin and 1.2 after. This trypsin concentration is still greater than "typical" for the disease (Table I). Amylase and lipase were comparably subnormal but not absent. Trypsin was present in the stool by the x-ray film test.

The infant returned home and received penicillin and streptomycin aerosol and intramuscular penicillin alternating with oral sulfamerazine in from one- to two-week periods. Pancreatin, low fat diet, and additional vitamin supplements

were also given. Her weight improved transiently to 5.4 kilograms, but deteriorated during respiratory exacerbations. After a trial of aureomycin she died at the age of 23 months.

A complete autopsy was done and established the diagnosis of cystic fibrosis of the pancreas. The gross findings of importance were limited to the lungs and the pancreas. All the rest of the organs were well formed and were not anomalous, either grossly or microscopically. The lungs seemed to be of fairly full volume, but nonetheless gave the impression of not being well aerated. They were mottled pink to reddish color, but this was not striking, and obvious inflammation was not grossly present. Upon sectioning, however, the bronchi were dilated and filled with a tenacious, apparently mucous, type of material. The *pancreas* was grossly of normal size. It presented no unusual characteristics except for being slightly firm in consistency. The usual lobulations were identifiable. The ducts were not carefully examined grossly.

Microscopically, the general pattern of the pancreas is well-preserved and the islet elements seem normal (Fig. 2). Nonetheless, there is extensive fibrosis throughout with detailed atrophy of many of the finer portions of each pancreatic lobule. The acini are usually dilated and lined by a relatively low type of epithelium containing very few or no zymogen granules. There is fibrosis around each acinus and as the ducts are approached there is sudden dilatation of these structures which show a corresponding, central, heavily staining material. Although at a low-power glance the fibrosis is not markedly advanced, nonetheless, careful examination reveals at least 60 per cent of the structurally functional portions of the pancreas to have advanced atrophic changes and fibrosis. The lungs show extensive bronchial and peribronchial inflammation with some necrosis of the wall. There is a low-grade inflammatory response that extends well out into the alveolar areas where a certain degree of macrophage and aspiration pneumonitis is encountered. No other specific abnormality is seen.

COMMENTS

The relationship of patients J. F. and J. N. to the normal range and to the usual fibrocystic range of pancreatic enzyme concentration of the duodenal fluid and the rise in the plain vitamin A absorption curve is shown in Table I. Values for four other fibrocystic cases that do not fit the usual group are also shown.

Zuelzer and Newton[8] have recently mentioned a case somewhat comparable to J. N. respecting trypsin. By Fermi's method, trypsin was found to be "20 per cent" but later was absent. It is anticipated that the present report will be reminiscent of other cases in which otherwise typical cystic fibrosis of the pancreas presented anomalous clinical laboratory findings.

The present cases indicate that the diagnosis of cystic fibrosis of the pancreas cannot be positively ruled out by normal vitamin A absorption curves or by trypsin concentration of the duodenal aspirate in the lower normal range. It seems probable that the infant bilumen tube used in conjunction with secretin may have a special usefulness in evaluating these cases of partial pancreatic deficiency.[10] There is, however, need of a diagnostic criterion, based perhaps on a defect in some mucolytic system and not dependent on pancreatic insufficiency.

These cases and their tests support the clinical and autopsy evidence not only that a partial degree of pancreatic deficiency in cystic fibrosis of the pancreas can occur, but that the structural lesions and impairment of function

tend to become more severe with passage of time. The existence of partial degrees of pancreatic deficiency tends to explain the good nutrition which some patients with cystic fibrosis of the pancreas can maintain without administration of pancreatin. It seems probable that, by minimizing gastric contamination, use of the bilumen gastroduodenal tube in the present study has disclosed higher enzyme concentrations than would otherwise have been detected.

SUMMARY

Two cases of cystic fibrosis of the pancreas, proved by autopsy, showed, during life, biochemical evidence that pancreatic achylia was not complete. In one case, two vitamin A absorption curves were in the normal range and a definite trace of trypsin was present in the duodenum at the age of 10 months. In the other, a trypsin concentration in the normal range was found at the age of 8½ months and trypsin concentration was still unusually high for this disease at age 14 months.

REFERENCES

1. Sinclair, W. Jr.: Cystic Fibrosis of the Pancreas, Ohio State M. J. **44**: 1024, 1948.
2. Kohl, H. W.: Fibrocystic Disease of the Pancreas, Arizona Med. **5**, No. 6: 47, 1948.
3. Pugsley, H. E., and Spence, P. M.: A Case of Cystic Fibrosis of the Pancreas Associated with Chronic Pulmonary Disease and Cirrhosis of the Liver, Ann. Int. Med. **30**: 1262, 1949.
4. Hellerstein, H. K.: Cystic Fibrosis of the Pancreas in the Adult, Ohio State M. J. **42**: 616, 1946.
5. Ross, R. A.: Case Records of the Massachusetts General Hospital, Case 34512, New England J. Med. **239**: 975, 1948.
6. Farber, S.: Pancreatic Function and Disease in Early Life, V. Pathological Changes, Arch. Path. **37**: 238, 1944.
7. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, Am. J. Dis. Child. **56**: 344, 1938.
8. Zuelzer, W. W., and Newton, W. A.: The Pathogenesis of Fibrocystic Disease of the Pancreas, Pediatrics **4**: 53, 1949.
9. Shwachman, H., Patterson, P. R., and Laguna, J.: Studies in Pancreatic Fibrosis: A Simple Diagnostic Film Test for Stool Trypsin, Pediatrics **4**: 222, 1949.
10. Gibbs, G. E.: a) Secretin Tests With Bilumen Gastroduodenal Drainage in Infants and Children, Pediatrics **5**: 941, 1950.
    b) Some Diagnostic and Therapeutic Techniques in Cystic Fibrosis of the Pancreas, California Med. **69**: 341. 1948

CEREBRAL BIRTH INJURY IN RETROSPECT

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ONE encounters in active children's clinics, more often than in private practice, children with developmental abnormalities or who have suffered injuries to their brains, which have resulted in mental retardation, convulsive disorders, or spastic paralysis. Referrals of such patients to medical centers is of frequent occurrence, either because of reluctance or inability of the physician to explain the situation to the parents or because of the unwillingness of parents to accept the verdict of their physician.

Whenever such a child is seen one seeks to ascertain the cause of his trouble, the time of deviation from the normal, and whether the condition might have been prevented. The consensus has been that most of the serious childhood cerebral abnormalities are the result of hereditary or of intrauterine developmental defects. Thus Yannet[1] found in a survey of 1,330 children with mental retardation a 38.5 per cent familial incidence of defect and a 21.5 per cent incidence of congenital defect. Only 3.2 per cent of the cases were attributed to brain injury. Nevertheless, a recurring viewpoint has been that birth injury (including anoxia) may be a major etiological factor in these difficulties. Cole[2] has estimated that mental retardation, with or without associated convulsive disorders and spasticity, may be due, in as high as 70 per cent of cases in children, to brain injury at birth.

Several exhaustive investigations have been made into causation, nature, and effects of the various forms of injury that a child might sustain in the course of birth. These injuries, traumatic or anoxic, are of significance in neonatal morbidity and mortality and may play a more important role than is generally suspected in etiology of later defects of physical and mental development.

Even the so-called "spontaneous deliveries" free of apparent complications have been associated with every known type of brain lesion. The quickly progressing and short labors, that prove so satisfactory to the mother, on the whole appear more dangerous for the infant. In every labor, and particularly in the case of the primigravida, as a result of necessary configuration of the infant's skull, brain tissues may be traumatized to a certain extent. In the majority of cases strain on the meninges and the compression of the brain remain within normal limits, although Russ and Strong[3] have shown that transient signs of minimal damage are not uncommon. Such signs include mild spasticity, nystagmus, opisthotonos, and delayed initial respiration in the immediate neonatal period. Our studies indicate that minor and seemingly insignificant changes may later attain a serious character.

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ANOXIA

Cole[2] and Schreiber[4] suggest that the most important cause of birth injury is anoxia and state that too much emphasis is placed on intracranial hemorrhage. Faber[5] supports this concept based on careful study of 99 cases of brain injury. He states that 75 per cent of the children investigated had the origin of their disorder in the prenatal or paranatal period. Thirty-five per cent of the injuries were a result of anoxia due to prenatal difficulty. Premature separation of the placenta was an apparent cause in 20 per cent of the patients whose difficulty arose in the prenatal period. The rapid onset and severe degree of anoxia resulting in marked brain damage due to this disorder have been pointed out by Clifford,[6] who also attributes the anoxia caused by placenta previa to premature separation in the process of labor.

Outstanding, as causes of anoxia in the paranatal period appear to be oversedation and excessive anesthesia during labor; a chief offender has been pointed out by Eastman[7] to be nitrous oxide anesthesia. He states that an 85:15 per cent nitrous oxide-oxygen combination, if inhaled by the mother for three minutes, will give rise to advanced anoxia in one out of three infants. Other forms of anoxia come from use of anesthetics that depress maternal blood pressure. Caudal and spinal anesthesia may lower the systolic blood pressure below 80 in 10 per cent of cases. Resting and contracting uterine tone is greater than 80 systolic so that fetal anoxia may result. Systemic disease in the mother, such as cardiac decompensation, pneumonia, and tuberculosis may give rise to lowered oxygen tensions in the blood reaching the placenta. Although anoxia in the mother may be "anoxic," stagnant, anemic, or cytotoxic, the end result on the fetus is the same. Eastman[7] also states that fetal mortality with placenta previa and massive placental infarction ranges from 65 to 90 per cent depending on the severity of the condition. Cases of survival would therefore show a high incidence of anoxic damage. Danger to infants of posterior pituitary extracts to initiate and speed up labor has been pointed out by De Lee.[8] They are still commonly used, and in case of overdosage and idiosyncrasy, produce prolonged tetanic contractions of the uterine musculature, resulting in collapse of uterine circulation and fetal anoxia. Conservative obstetrical opinion is that the drug should be used only in cases of true uterine inertia.

Clifford[9] has found that anoxic injury is the primary cause in 60 per cent of the deaths in full-term and premature babies and at least that amount of morbidity among neonatal defectives. He has shown that anoxia, by generating the lactic acid cycle, causes excess degrees of excitation due to lowering of the pH value. Maximal excitation predisposes to nervous exhaustion. This may be the basis of the frequent petit mal variant electroencephalographic dysrhythmia so often seen in infants following anoxia. Acidosis also predisposes to hemorrhage and plasma leakage giving rise to cerebral edema.

Anoxia in utero, according to Clifford,[6] causes the fetus to aspirate amniotic fluid. This gives rise to further postnatal difficulty in the form of poor respiratory exchange due to failure of the alveoli to open or due to spotty atelectasis and may account for the high degree of fetal mortality and morbidity, following cesarean section. Clifford,[9] in 1934, reported a mortality rate of 54 per cent in

infants weighing less than 5 pounds delivered by cesarean section. His suggestion was that anesthetic suppression, with ether in particular as an offender, was the cause. Change of anesthetic was followed by a reduction to a 16.5 per cent mortality.

Russ and Strong[3] observed that many infants were delivered by cesarean section with the idea in mind that the procedure would afford protection to the infant. In a large series of elective sections they found that this was not true. The average death rate of infants born by cesarean section at all weights of fetus was 9 to 10 per cent. This included, however, elective and emergency sections. In cases showing morbidity, the infants appeared to be in good condition for several hours except for perhaps slight grunting respirations, then cyanosis and respiratory distress developed. Attacks were recurrent resulting either in death or marked anoxia. Post-mortem findings revealed expansion of alveoli, but the alveolar walls were observed to be covered with a pseudomembrane of amniotic fluid and its ectodermal contents. Tracheal aspiration following normal deliveries produced from 1 to 2 c.c. of fluid while an average of from 3 to 7 c.c. was recovered from babies born by cesarean section. The cause of aspiration was thought to be asphyxia.

Anoxia may cause damage to the respiratory center resulting in edema and an ensuing cycle of further depression. The cardiac center may also become involved to produce stagnation of the circulation according to Schnedorf and associates.[10] Concussion type of effect, as a result of increased pressure in the birth canal or precipitous delivery may also account for medullary damage. Denny-Brown and Russell[11] have shown that concussion injuries affect predominantly the lower centers. A theory of shearing forces (as an explanation of concussion) produced by marked increased pressure has been developed by Ward and associates.[12] Such a theory may explain the pathologic physiology behind respiratory and circulatory failure in the newborn infant without associated medullary hemorrhage.

Prolapse of the umbilical cord, occurring once in every 150 deliveries (according to Eastman[7]), is very difficult to treat and usually requires as rapid delivery as possible. Ehrenfest[13] has pointed out two other forms of cord constriction. Abnormal twisting or wrapping of the cord about the neck is not uncommon but cannot be corrected. He does point out, however, the marked dangers of holding the head back in the final stages of delivery when the head is on the pelvic floor. This common offense of nurses, to prevent delivery until the physician arrives, is said to produce cord constriction and therefore marked anoxia.

Depressant drugs giving maternal analgesia also are well-known offenders in producing fetal depression and delayed initiation of respiration. These compounds are still used to a large extent and even the milder sedatives have been shown to produce a depressing effect. Smith[14] has found that morphine and scopolomine will produce asphyxia in 50 per cent of newborn infants, whereas morphine alone will give the effects in 33 per cent of infants. Demarol has been shown by Black[15] to result in 5.5 per cent neonatal morbidity with varying degrees of asphyxia. Hughes, Ehemann, and Brown,[16] in a careful study of a

large series of newborn infants by electroencephalography, have found a high incidence of electrical depression, and to a lesser degree clinical depression, following the use of Seconal during labor. These workers found that the electroencephalogram was a sensitive indicator of cortical depression produced by Seconal sedation. The basic rhythm reflected by such sedation was a low voltage pattern in contrast to a higher voltage, 1 to 2 per second rhythm normal for the immediate neonatal period. The latter pattern was observed in infants of mothers receiving no sedation during labor. Low voltage rhythm was associated with clinical drowsiness and lethargy and was observed to persist one to two days after return of normal clinical signs. In correlation with a story of birth injury, Hughes and associates,[16] did an electroencephalographic follow-up study of seven newborn infants with findings of both focal and generalized dysrhythmia. These included reports of two severely anoxic infants, apparently a result of heavy sedation of the mother during labor. Both infants showed generalized low voltage depression of rhythm for several days. They concluded that even the so-called more benign sedatives predisposed to cerebral and therefore respiratory depression.

Clifford[6] suggested that placental pathology in erythroblastosis fetalis, resulting in hypoxia, might give rise to brain damage. Eighty-six per cent of cases of icterus gravis type of erythroblastosis showed placental changes consisting of increased size of villi, syncytial degeneration, epithelial vacuolization, hyperplastic or edematous stroma, and diminution of vessels. A greater number of cases of kernicterus from erythroblastosis, according to Diamond and coworkers[17] occur after premature deliveries. It was their belief that increased susceptibility to brain injury was the cause.

The incidence of stillbirth, neonatal death, and birth injury have been found in the same hospital to be higher in infants born at term to toxemic mothers than in full-term infants of nontoxemic women. Brash[18] states that the principal cause is a greater liability to asphyxia resulting from antepartum hemorrhage and placental infarction. He found no post-mortem evidence that toxic changes in the fetus occurred as a direct result of toxicity within the mother. There was a higher incidence of neonatal edema including the brain. Drillien[19] has found that toxemia of pregnancy predisposes to prematurity.

Animal experimentation supports the concept of permanent cerebral damage as a result of fetal anoxia. Fender, Neff, and Binger,[20] simulated in dogs those conditions which occur in fetal life and at birth in association with oxygen deprivation to the fetus. Pregnant bitches in the last week of pregnancy were subjected to an atmosphere with an oxygen content below 4 per cent for twenty to thirty minutes. Carbon dioxide was not allowed to accumulate. One dog aborted. Twenty-five pups born from twenty-four to seventy-two hours after the anoxia died during the first week of life. Several animals developed status epilepticus at the end of a month. Autopsies showed only signs that could be attributed to anoxia. The authors felt that a definite relationship existed between anoxia of the newborn infant and later convulsions. Windle[21] compared the behavior of guinea pigs in which anoxia that had been produced, by clamping off the uterine vessels, with that of normal litter mates. Brain damage was found to be directly proportional to the asphyxia.

CLINICAL PATTERN AFTER ASPHYXIA

Anoxia of long duration before birth is recognized by golden yellow vernix caseosa and yellow staining of the skin and nails of the newborn infant. The infant who has had mild asphyxia at birth may appear to be in fair condition for several hours. Slight grunting respirations and slight cyanosis of the extremities may later become more marked with severe respiratory distress and dilatation of the alae nasi. Periodic attacks of apnea, a feeble cry, a hypotonic state, poor sucking reflex, or absent deep reflexes may be noted. Many infants show petechial hemorrhages and ecchymoses. Gross bleeding, by emesis or by rectum is not uncommon. Increased intracranial pressure, a result of cerebral edema and central nervous system damage may be manifested by convulsions, coma, and irregular respirations.

BIRTH TRAUMA

In the course of normal and particularly of abnormal birth, the cranial contents may be traumatized without coincident damage to the skull. In the second stage of labor necessary changes in the configuration of the fetal head are made possible by the bending of the elastic cranial bones and by over-lapping at the sutures. The value of such molding comes not in reduction of the cranial size but rather in changes of shape to fit the configuration of the pelvic canal. Reduced intracranial size may result from escape of cerebrospinal fluid into the spinal canal but also from reduction in cerebral blood flow. In general, the infant is free of harm from the standpoint of compression only if alterations in cerebral circulation are neither excessive nor unduly prolonged.

Cephalopelvic disproportion is one of the major causes of cerebral damage during the natal process. Excessive molding in one diameter frequently results in dural tearing and therefore intracranial hemorrhage. Reduction in circulation may give rise to anoxia which also predisposes to hemorrhage. Such pelvic abnormalities serve as indication for elective cesarean section.

Large intracranial hemorrhages are of rare occurrence and are usually fatal. Small diffuse hemorrhages throughout the brain tissue apparently are produced by a suction effect on the head, created, after rupture of the membranes, by the difference between the higher intrauterine pressure and the lower atmospheric pressure in the area of the dilated cervix. This abnormal pressure relationship produces the well-known caput succedaneum but affects as well the veins of the underlying meninges and brain.

Gross evidence of intracranial trauma is present in only about one-half of the post-mortem examinations of infants dying as a result of prolonged, difficult, or precipitous labor. Denny-Brown and associates,[11] and Ward[12] explain the symptomatology on the basis of concussion where visible pathology is minimal and physiologic alterations of the vasculature, respiration, and basic neurological reflexes have occurred during life. The latter states that damage may be due to actual shearing forces resulting from acute positive and negative pressures. Damage is created chiefly in the lower centers.

With increasing use of forceps, evaluation should be made of the possible injurious complications resulting from instrumentation. Eastman[7] has found

that high forceps operations carry a 65 per cent mortality and midforceps operations a 30 per cent mortality to say nothing of morbidity. An investigation was made by Balf[22] of behavior at various levels of infants born by spontaneous delivery as compared with infants born by forceps delivery, in an attempt to determine the relationship of neonatal abnormalities to later physical and mental defects. Examination was restricted to full-term infants weighing between 5½ and 10 pounds. Systematic examination in the first two days showed minimal evidence of cerebral disorders in 5.9 per cent of infants born by spontaneous deliveries and 23 per cent of infants born by forceps deliveries. These figures corresponded well with the obstetrical history and the signs of fetal distress noted in the infant. Persistent vomiting was noted in 20 per cent of babies born by abnormal deliveries but in only 1 per cent of the normally delivered babies. The Moro reflex was found to vary or be absent along with loss of sucking and rooting reflexes. There was often no other evidence of cerebral irritation than vomiting and poor sucking. Day to day variations of body temperature were greater after instrumental delivery. Fever on the second and third days, associated with dehydration, was far more frequent after forceps delivery, even if special attention was given to fluid balance.

Subdural hematoma is a complication of traumatic birth that, if recognized in time, can often be remedied and its sequelae prevented. Ingraham[23] has reported that in a series of ninety-eight cases of subdural hematoma, twenty-eight could be traced back to the neonatal period.

INCIDENCE AND SEQUELAE OF BIRTH INJURY

The incidence and sequelae of birth injury are difficult to define. True objectivity has proved almost impossible to attain. Lack of uniformity in statistics of obstetrical technique gives rise to a wide range of estimates, while standardization of pathologic picture and criteria for diagnosis of birth injury have never been accomplished among various medical centers. The defensive attitude toward birth injury on the part of many physicians is understandable but not easily changed, since the condition may carry connotation to the family that could precipitate trouble. Furthermore, various neonatal disturbances such as cyanotic attacks, absence of sucking reflex, and listlessness often cannot be attributed to birth trauma. Obstetricians handle wisely and without reservation birth trauma of the pelvic outlet. If brain injury to the infant could be accepted in the same spirit, relationship between such injury and postnatal syndromes with early or late evidences of cerebral disturbance could be more clearly defined.

Our study has been prompted by the necessity of developing criteria for selection of patients for trial of carotid jugular anastomosis.[24] The procedure which is under evaluation has proved moderately effective in 35 to 40 per cent of patients.[25] However, one should seek better means of selecting the patients who may be benefited before subjecting them to surgery. On theoretical grounds less benefit should be expected for children with hereditary cerebral defects or with developmental abnormalities of their brains than in those children entirely normal up to the time of cerebral injury, from either trauma or infection. Thus

far, operation has been restricted to patients in the latter category, hence the necessity for careful study to establish if possible the underlying cause of the child's condition. Also, from the review of the mechanisms responsible for birth trauma it would seem that those children whose brains have been injured by anoxia should derive less benefit from the operation than those in whom vascular damage may have occurred as a result of direct trauma.

We have, in the past sixteen months, subjected to analysis 419 children with mental retardation, convulsive disorders, and cerebral palsy, singly or in combination.

METHOD OF EVALUATION

A total of 419 children ranging in age from 8 months to 14 years has been studied. Special attention was given to obtaining a careful history. Thorough physical and neurological examinations followed. On the basis of history and physical examination a classification of probable diagnoses was made. In about one out of five cases there was insufficient evidence to support even a probable diagnosis and those cases were classified as etiologically obscure. The classification is presented in Table I.

TABLE I. CLASSIFICATION OF CAUSE OF MENTAL RETARDATION, CONVULSIVE DISORDERS, OR CEREBRAL PALSY IN 419 CHILDREN, BASED ON HISTORY AND PHYSICAL EXAMINATION

	NO. OF CASES	% OF TOTAL
Birth injury (late prenatal and paranatal	218	52
Hereditary disease including postnatal	17	4.5
Congenital defects—developmental anomalies	13	3.2
Mongolism	24	6
Postnatal injury	57	14
Unknown	76	18.5
Kernicterus	7	1.8

Over one-half of the patients had a story strongly suggestive of birth injury while in about one out of six cases the difficulty could be traced to postnatal injury on a traumatic, infectious or degenerative basis. In only one out of six in our study did the finding suggest an hereditary or congenital defect as the cause of neurological difficulty. Mental retardation was found in 89 per cent, convulsive disorders in 47 per cent, and cerebral palsy in 42 per cent of the patients.

Excluding those of obviously severe idiocy, 172 cases of probable birth injury were studied by pneumoencephalography, electroencephalography, and psychometric examination. Forty-five of the cases of undeterminable etiology and 13 children with a diagnosis of postnatal injury also received this type of investigation. Pneumoencephalograms were examined for signs of generalized or localized cortical atrophy. Without some evidence of atrophy one could not assume that the brain had been normal up to the time of injury. Moderate and marked degrees of cortical atrophy are illustrated in Fig. 1. An attempt was made by electroencephalography to ascertain the presence of so-called cerebral dysrhythmias on an "organic" basis. A marked delta dysrhythmia or a petit mal variant dysrhythmia, as illustrated in Fig. 2, was selected as probably indicative of cortical damage. Epileptogenic foci were deemed more definite evidence

Fig. 1.—Pneumoencephalograms showing diffuse cortical atrophy following brain injury.

of cortical damage. Psychometric examination included measurement of intelligence with the use of the Gesell developmental schedules in children below a mental age of 2 years. The Minnesota preschool scale was used in the mental range of 2 to 4 years and the revised Stanford-Binet test was used in children above the 4-year achievement level. Where practical in the older children, the Cornell-Coxe performance ability scale, the Thematic apperception test and the child Rohrschach were used to help detect the presence of an organic rather than a functional cause for the retardation. Cerebral blood flow and cerebral metabolism studies were done in 22 cases of probable birth injury, 8 patients with postnatal injury, and four children with unknown cause of their pathology. This was done after the method described by McKhann, Belnap, and Beck.[25]

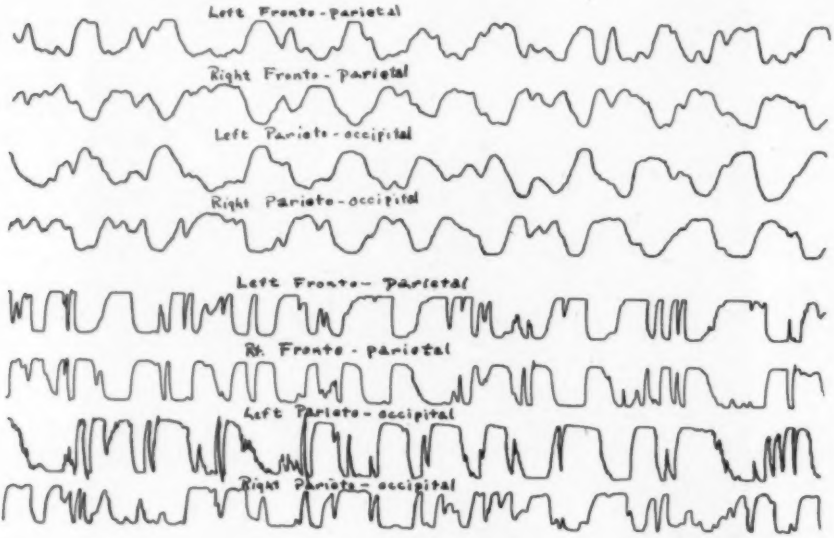

Fig. 2.—Petit mal variant and severe delta dysrhythmias indicative of organic brain change.

Solomon, Jasper, and Bradley[26] reported a high incidence of electroencephalographic dysrhythmias "on an organic basis" among behavior-problem children. Rosenfeld and Bradley[27] have suggested that the majority of these children have a history compatible with the diagnosis of birth injury. These reports prompted a careful study of our own of thirty-seven severe behavior-problem children. Eight of these children had pneumoencephalograms and all of them had electroencephalograms and complete psychometric studies in an attempt to ascertain the presence of an underlying organic cause. Most of the children had been found to be refractory to psychotherapy.

RESULTS AND DISCUSSION

The incidence of diffuse and localized cortical atrophy noted in pneumoencephalograms has been classified in all cases. In electroencephalograms only

the so-called severe or "organic" dysrhythmias were accepted as evidence of organic disorder because patients with practically all types of amentia may have an abnormally slow rhythm. Findings in patients with a history of neonatal cyanosis, in whom etiological basis was not clear, were classified separately from those of unknown etiology without a history of neonatal cyanosis. These findings are listed in Table II.

TABLE II. PNEUMOENCEPHALOGRAPHIC AND ELECTROENCEPHALOGRAPHIC FINDINGS IN THE 230 CASES

	NO. OF CASES	CORTICAL ATROPHY (%)			ORGANIC E.E.G. (%)
		DIFFUSE	LOCALIZED	TOTAL %	
Birth injury	172	79	21	87	89
Cause unknown with neonatal cyanosis	24	76	17	81	88
Cause unknown without neonatal cyanosis	21	51	15	56	69
Postnatal injury	26	82	29	93	94

A total of 87 per cent of patients in whom a diagnosis of probable birth injury could be made showed signs of either diffuse or localized cortical atrophy, and in several cases, both. It is interesting to note that a similarity of statistics is to be found between patients having a history of neonatal cyanosis without a history of definite birth injury and those with such a history. Perhaps just as important, however, is the observation that over one-half of the patients in whom a diagnosis of birth injury could not be made by history or suspected by presence of neonatal cyanosis had signs of cortical atrophy. The presence of postnatal cyanosis suggests that even a larger percentage of patients than indicated by birth history alone have a probable origin of their difficulty in birth injury. We are supported in this view by the close correlation between the x-ray findings and electroencephalographic results in cases definitely and presumptively due to birth injury. Moreover the analogy with observation in patients with postnatal injury is striking. More than nine out of ten patients with postnatal injury had signs of cortical atrophy and an associated severe dysrhythmia.

Cerebral blood flow studies showed a marked reduction of flow in cubic centimeters per 100 Gm. of brain tissue per minute from an average of 72 in a control series of ten normal children to 43 c.c. per 100 Gm. of brain tissue per minute in the twenty-two children with a diagnosis of probable birth injury. In all but two cases the flow was subnormal in the above group while seven of the eight children with postnatal brain injuries demonstrated the same findings. Although not a statistically significant series, two of the four cases in which etiology was not determined gave similar results. This marked reduction in total flow may be explained on the basis of gliosis associated with and subsequent to brain injury. Penfield[28] has shown a marked deficiency of capillary bed to exist in the presence of gliosis, thus resulting in a diminished circulation. We have been unable to find any reduction in blood flow with similar studies of five children with mongolism.

Psychometric examination excluded the diagnosis of functional or pseudo-retardation from the series and supported the concept of a high degree of "organicity" in all cases. The ranges of I. Q. in the cases of probable birth injury and of unknown etiology are presented in Table III. A very close correlation was observed between the reduction in I. Q. and the severity of the injury as indicated by cortical atrophy and electroencephalographic dysrhythmia.

TABLE III. I. Q. DISTRIBUTION OF THE 172 PATIENTS WITH BIRTH INJURY AND 45 CASES OF UNKNOWN DIAGNOSIS

	<30		30-50		50-70		70-90		90	
	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL
Birth Injury	31	18	51	29.5	47	27	39	22.5	3	1.7
Unknown Causes	3	6.5	18	40	16	36	7	15.5	0	0

On the basis of the supporting evidence we assumed the probability of birth injury in the 172 cases. They have been broken down into prenatal and paranatal groups depending upon the time of possible onset of the trauma. The number of cases in each group and their percentage of the total have been tabulated. In Table IV are listed the probable causative and contributory factors in the prenatal period.

TABLE IV. PROBABLE CAUSATIVE AND CONTRIBUTORY FACTORS IN THE PRENATAL PERIOD

	NO. OF CASES	% OF TOTAL (172 CASES)
Premature separation placenta	7	4
Placenta previa	5	3
Kernicterus	7	4
Prematurity	27	15.5
Oversized infant (greater than 3,800 grams)	6	3.5
Toxemia	9	5
Maternal illness (anoxia)	6	3.5

Although prematurity is mentioned as a prenatal factor, most of the difficulty contributing to brain injury in this group probably arose during the birth process and in the neonatal period as a result of anoxia secondary to poor control of respiration. In the active prenatal period placental separation ranked highest as a cause of injury. Toxemia of pregnancy and kernicterus, the resulting mental defects of which may be secondary to placental abnormalities, also ranked high. We found that oversize (over 3,800 grams) may have been a cause in six of our cases and maternal illness resulting in anoxia, the cause in an equal number.

Table V lists the probable causation and contributory factors in the paranatal period.

Marked sedation and "heavy" anesthesia appeared as possible causes of 17 per cent of our birth injuries. The chief offender was morphine or morphine in combination with scopolomine. In most cases there was a story of the mother being "asleep" during the entire labor and of a slow initiation of respiration

TABLE V. PROBABLE CAUSATIVE AND CONTRIBUTORY FACTORS IN THE PARANATAL PERIOD

	NO. OF CASES	% OF TOTAL (172 CASES)
Prolonged labor	7	4
Prolonged and "heavy" anesthesia	10	6
Marked sedation	19	11
Induced labor (oxytocic)	5	3
Breech delivery	7	4
Cesarean section (elective and emergency)	14	8
Cord defects		
(a) prolapse	2	1
(b) holding back of head	17	10
(c) tight about neck	9	5
High forceps	5	3
Precipitous delivery	9	5

in the infant. Prolonged anesthesia in the second stage of labor may not be a singular cause. Some difficult and possibly traumatic deliveries may necessitate the use of prolonged anesthesia. A story of neonatal cyanosis was present in the majority of infants so delivered. Second in prominence within our series was a story of the head being held back by the nurse or intern until the physician arrived. This is a common practice, and certainly if cerebral injury resulted frequently, the incidence of brain injury would be enormous. As was pointed out in the introductory discussion, trauma due to increased intracranial pressure is probably not the mechanism of this type of injury but rather compression of the cord in the birth canal. We are unable to say that all seventeen of our cases with such a history were secondary to "head holding," but a history of neonatal difficulty compatible with a story of cerebral injury was obtained in all but two of the seventeen. With cesarean section, the question arises as to the cause of brain damage. Once again difficult delivery requiring emergency section may be the primary cause and the anesthesia only secondary. Nine of our fourteen patients with a story of a stormy neonatal course were a result of elective cesarean sections in which asphyxia may have been a primary cause. All five of the patients, in whom labor was induced by the use of oxytocic drugs, experienced a precipitous labor and delivery. Noteworthy is the high incidence of focal atrophy and focal dysrhythmia among the several cases of high forceps delivery and precipitous delivery, suggesting that localized contusion or hemorrhage may have occurred.

Careful examination of the histories of the thirty-seven behavior-problem children revealed a significantly higher incidence of a story suggesting birth injury than is true of the normal population. Such a history was given for 36 per cent of the children and 8 per cent had a story of postnatal injury. There was no family history of mental defects and in none were congenital defects apparent. This classification is presented in Table VI.

TABLE VI. CLASSIFICATION OF 37 PATIENTS WITH SEVERE BEHAVIOR PROBLEMS, AS TO DIAGNOSIS, BASED ON HISTORY AND PHYSICAL EXAMINATION

	NO. OF CASES	% OF TOTAL
Birth injury	13	36
Postnatal injury	3	8
Familial history	0	0
Unknown	21	56

These children ranged in intelligence from 80 to 135, the majority being within limits of normal intelligence. All of the children had received some psychotherapy and several extensive therapy over a one- to two-year period. As a whole, they appeared to be refractory to such therapy. Careful studies were made to determine an accurate I. Q.; the range of all the children is found in Table VII.

TABLE VII. I. Q. DISTRIBUTION OF THE 37 PATIENTS WITH BEHAVIOR DISORDERS

80-90		90-100		100-110		110-120		>120	
NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL
8	22	12	33	9	25	6	16.5	1	2.7

Careful testing was done to determine the presence of an "organic" component to the personality disorder. Electroencephalograms were done in all cases to determine the presence of any dysrhythmia before or during hyperventilation of the patient. Patients with only a hyperventilation dysrhythmia were classified as having an electroencephalographic abnormality despite the known existence of such dysrhythmias in 10 per cent of the "normal" population. In Table VIII are found the electroencephalographic and psychometric results of all the patients. Prominent is the incidence of dysrhythmias and abnormal psychometrics among the cases with a story of brain injury. Just as significant, however, is the existence of such findings, even though to a less degree, among children without a history of brain injury. Focal dysrhythmias in all groups were infrequent. The total patients having dysrhythmias in the series of 37 was 65 per cent, and those having abnormal psychometrics 52 per cent.

TABLE VIII. EEG AND PSYCHOMETRIC FINDINGS IN 37 BEHAVIOR-PROBLEM CHILDREN

	NO. OF CASES	% OF TOTAL	EEG DYSRHYTHMIAS (%)	"ORGANIC" PSYCHOMETRICS (%)
Birth injury	13	36	84	65
Postnatal injury	3	8	100	66.6
Unknown	21	56	45	38

Total having EEG dysrhythmia = 65%
Total having "organic" psychometric = 52%

These findings support those of Preston[29] who reviewed the histories of 132 children with anoxia at birth in relation to a long range follow-up. One-fourth of these were mentally retarded. The remainder were normal mentally but showed deviate behavior. Twenty per cent of the children had convulsive disorders. Many of his patients, as well as of our own, presented feeding problems in the first year of life and were falsely classified as cases of "cyclic vomiting." Some children are hyperkinetic while others are apathetic, but particularly distressing is the inability of bright children to concentrate or cooperate.

Solomon and associates[26] have found that the type of dysrhythmia is usually generalized and slow and is rarely focal. In a large series of carefully studied

cases these authors concluded that the abnormality was an underlying organic defect. Organic brain damage could produce such dysrhythmias and a positive correlation existed with such findings and a history of birth injury. In a series of 160 children with all degrees of behavior disorders they found an incidence of 35 per cent dysrhythmia. Rosenfeld and Bradley,[27] in another series of 673 children referred for psychotherapy, found a 40 per cent incidence of abnormal electroencephalograms. The majority of those having a history of neonatal asphyxia showed a characteristic syndrome consisting of fluctuations in mood, hyperkinesis, short attention-span, impulsiveness, fluctuant ability to recall previously learned material, and conspicuous difficulty with arithmetic.

As an aid to further diagnosis of birth injury we have tabulated the seven most common signs of abnormality encountered in the neonatal period. They have been listed by percentage and in the order of their frequency in Table IX. Particularly prominent was the failure to suck and the marked lethargy.

TABLE IX. NEONATAL SIGNS IN ORDER OF THEIR OCCURRENCE BY HISTORY

SIGNS	OCCURRENCE (%)
Poor sucking reflex	92
Poor rooting reflex	86
Lethargy	76
Cyanosis	68
Vomiting	64
Convulsions	47
Variation in body temperature	36

SUMMARY

As surgical and medical procedures come under evaluation in therapy of children with mental retardation, convulsive disorders, cerebral spasticity, and behavior problems, the selection of patients for various types of treatment may depend on the etiology of the child's condition. Thus in selecting patients for carotid jugular anastomosis, less benefit should be expected on theoretical grounds for children with congenital cerebral defects or developmental abnormalities of their brains than in those children entirely normal up to the time of cerebral injury either from trauma, anoxia, or infection. Hence, the necessity of better means of determining causative factors in cerebral disturbances. We have reviewed a series of cases, seeking to determine the incidence of birth injuries as a cause of late cerebral disorders. The evidence suggests that birth injuries may be a major factor in their causation. Studied in retrospect, the evidence does not distinguish between cerebral birth injuries due to anoxia and those due to direct trauma. Cortical atrophy revealed in pneumoencephalograms is accepted as presumptive evidence that the brain was injured following complete formation. This finding, together with changes attributable to organic disease in the electroencephalographic tracings, was present in almost all patients with a known history of birth injury and in an unsuspectedly large number of other children in whom the history was obscure. Decreased cerebral blood flow was present in those cases studied in whom gliosis might have followed cerebral injury, but was absent in children with a known developmental defect as exemplified by mongolism.

Behavior disorders in children without retardation, spasticity, or convulsions appear to be possible sequelae of milder degrees of cerebral injury at birth. The data suggest that at least one out of five of birth injuries may have been due to preventable causes.

REFERENCES

1. Yannet, H.: Diagnostic Classification of Patients With Mental Deficiency, Am. J. Dis. Child. **70:** 83, 1945.
2. Cole, W. C. C.: Asphyxia During Delivery and Immediately Post Partum (Discussion), J. PEDIAT. **19:** 258, 1941.
3. Russ, J. D., and Strong, R. H.: Asphyxia of the Newborn, Bol. méd. d. Hosp. inf., Mexico **5:** 27, 1948.
4. Schreiber, F.: Anoxic Considerations in Diagnosis and Treatment of Craniocerebral Injuries, Indust. Med. **11:** 383, 1942.
5. Faber, H. K.: Cerebral Damage in Infants and Children, Am. J. Dis. Child. **74:** 1, 1947.
6. Clifford, S. H.: Fetal Anoxia at Birth and Cyanosis of the Newborn, Am. J. Dis. Child. **76:** 666, 1948.
7. Eastman, N. J.: Prevention of Fetal Anoxia, Am. J. Dis. Child. **76:** 661, 1948.
8. De Lee, J. B.: Use of a Solution of Posterior Pituitary in Obstetrics, J. A. M. A. **115:** 1320, 1940.
9. Clifford, S. H.: Reduction of the Premature Infant Mortality, J. PEDIAT. **5:** 139, 1934.
10. Schnedorf, J. G., Munslow, A. B., Crawford, R. J., and McClure, R. D.: Birth Anoxia and Oxygen Therapy, Surg., Gynec. & Obst. **70:** 628, 1940.
11. Denny-Brown, D., and Russell, W. R.: Experimental Cerebral Concussion, Brain **64:** 93, 1941.
12. Ward, G. W., Montgomery, L. H., and Clark, S. L.: A Mechanism of Concussion: A Therapy, Science **107:** 349, 1948.
13. Ehrenfest, H.: Birth Injuries, chap. 6, in Gynecology and Obstetrics, C. H. Davis, ed., Hagerstown, Md., W. H. Prior Company, Inc., 1949.
14. Smith, C. A.: Physiological Mechanisms of Fetal Anoxia at Birth and Cyanosis in the Newborn, Am. J. Dis. Child. **79:** 1, 1950.
15. Black, M. L.: Personal communication.
16. Hughes, D., Ehemann, B. C., and Brown, L.: Electroencephalography of the Newborn, Am. J. Dis. Child. **76:** 620, 1948.
17. Diamond, L. K.: Erythroblastosis Fetalis or Hemolytic Disease of the Newborn, Proc. Roy. Soc. Med. **40:** 546, 1947.
18. Brash, A. A.: Effects of Toxemia of Pregnancy on Fetus and Newborn Child, Arch. Dis. Childhood **24:** 107, 1949.
19. Drillien, C. M.: Toxemia of Pregnancy. Studies in Prematurity, Stillbirth, and Neonatal Death, J. Obst. & Gynaec. Brit. Emp. **54:** 300, 1947.
20. Fender, F. A., Neff, W. B., and Bingera, G.: Convulsions Produced by Fetal Anoxia; Experimental Study, Anesthesiology **7:** 10, 1946.
21. Windle, W. F.: Structural and Functional Alterations of the Brain Following Neonatal Asphyxia, Psychosom. Med. **6:** 155, 1944.
22. Balf, C.: Neonatal Behavior of Infants Born by Spontaneous and Forceps Delivery, Arch. Dis. Childhood **23:** 142, 1948.
23. Ingraham, F. D., and Matson, D. D.: Subdural Hematoma in Infancy, J. PEDIAT. **24:** 1, 1944.
24. Beck, C. S., McKhann, C. F., and Belnap, W. D.: Revascularization of the Brain Through the Establishment of a Cervical Arteriovenous Fistula, J. PEDIAT. **35:** 317, 1949.
25. McKhann, C. F., Belnap, W. D., and Beck, C. S.: Cervical Arteriovenous Anastomosis in the Treatment of Mental Retardation, Convulsive Disorders, and Cerebral Palsy, Ann. Surg. (In Press).
26. Solomon, P., Jasper, H., and Bradley, C.: Studies in Behavior Problem Children, J. Nerv. and Ment. Dis. **86:** 459, 1937.
27. Rosenfeld, G. B., and Bradley, C.: Childhood Behavior Sequelae of Asphyxia in Infancy, Pediatrics **2:** 74, 1948.
28. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization, Springfield, Ill., 1941, Charles C Thomas.
29. Preston, M. L.: Late Behavioral Aspects Found in Cases of Prenatal, Natal, and Postnatal Anoxia, J. PEDIAT. **26:** 353, 1945.

THE GLYCEMIC RESPONSE OF THE NEWBORN INFANT TO EPINEPHRINE ADMINISTRATION: A PRELIMINARY REPORT

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LOW glucose levels in the blood of newborn and premature infants have been noted with a fair degree of regularity.[1-4] Since glycogen has been demonstrated in liver tissue from animal and human fetuses[5] and from stillborn infants, this observation is all the more intriguing. Van Crevald in 1929,[1] and Hartmann and Jaudon in 1937,[2] suggested that the hypoglycemia observed in newborn infants might be attributed to a primary difficulty in the mobilization of the liver glycogen available.

The present investigation was undertaken to find what relationship exists between the infant's fasting blood sugar level and the blood sugar level after epinephrine administration. The purpose of the study was twofold: (a) to determine the rapidity and degree of glycogenolysis in the newborn infant; and (b) to determine whether the glycemic response to epinephrine is sufficiently consistent to be of use as a liver function test during the neonatal period.

PLAN OF STUDY

1. Subjects.—The subjects were normal full-term infants in the newborn nurseries of Hermann Hospital, Houston, Texas. Infants suspected of disease and infants born of ill mothers were excluded from this study. A total of sixty-nine infants was studied.

The infants were kept on a routine regime, i.e., water was offered twelve hours after birth and the infant put to breast or on formula twenty-four hours after birth. No carbohydrate feedings were given. Fasting specimens were not taken until the body temperature had reached 98.2° F. Infants older than twenty-four hours were fasted for a seven-hour period prior to the test. During test periods water was given freely.

2. Methods.—Blood glucose was determined by the Lauber-Mattice micromethod, which is a true sugar method, utilizing zinc hydroxide precipitation followed by Folin-Wu copper sulfate reduction on the protein-free filtrate. Determinations were made with the Evelyn photoelectric macrocolorimeter. Blood for glucose determination was obtained by heel puncture employing a No. 11 Bard-Parker blade. Each determination required one-tenth of a cubic milliliter of capillary blood.

3. Procedure.—After the fasting specimen had been obtained, epinephrine (0.03 ml. of 1:1,000 epinephrine hydrochloride per kilogram body weight), was

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injected subcutaneously or intramuscularly. Specimens were taken at half-hourly intervals for a three-hour period thereafter. In some of the earlier subjects, specimens were taken for a two-hour period only. Throughout the experiment, manipulation of the infant was kept at a minimum.

The sixty-three infants to whom epinephrine was administered, were divided into groups according to age and route of administration of epinephrine. In seven of these infants, the test was repeated at a later age. As a control group, six infants were subjected to the same procedure, without administration of epinephrine.

RESULTS

The results obtained are tabulated in Charts I to V and in Tables I to III. Almost all the infants studied showed some increase in the blood glucose level following epinephrine administration. The mean rise in blood sugar in all groups is higher than that noted in the control group. The extent of the glycemic response is, however, extremely variable, as is seen by the large standard deviations* from the mean peak rise (Table I) and by the individual curves depicted in Charts I through IV.

TABLE I. MEAN RISE IN BLOOD GLUCOSE FOLLOWING EPINEPHRINE ADMINISTRATION IN INFANTS GROUPED ACCORDING TO AGE AND ROUTE OF ADMINISTRATION

AGE OF INFANT AND ROUTE OF ADMINISTRATION	NUMBER OF CASES	MEAN PEAK RISE IN BLOOD GLUCOSE MG./100 C.C.	STANDARD DEVIATION
Birth to 24 hrs.			
Epinephrine subcutaneously	12	37	±17
Epinephrine intramuscularly	14	51	±16
24 to 48 hours			
Epinephrine subcutaneously	6	56	±17
Epinephrine intramuscularly	7	53	±24
48 to 96 hours			
Epinephrine subcutaneously	10	54	±36
Epinephrine intramuscularly	6	47	±17
5 to 10 days			
Epinephrine subcutaneously	5	63	±25
Epinephrine intramuscularly	3	60	±14

In the individual infant the height of rise in blood glucose following epinephrine administration cannot be predicted from the height of the fasting level. In this small group of full-term infants the rise in blood glucose could not be correlated with birth weight, nor in the case of infants less than 24 hours of age, with the length of the fasting period.

In Charts I to IV the epinephrine tolerance curves are grouped according to age of the infant and the route of administration of the drug. From these it is seen that the 5- to 10-day-old group tends to have a higher fasting blood glucose level than the younger groups, a finding noted repeatedly by other workers. This group also shows a greater height of peak rise in blood glucose level after epinephrine than that shown in the younger infant groups.

*$\sigma = \sqrt{\frac{\Sigma (V - M)^2}{N}}$

TABLE II. TIME OF PEAK RISE IN BLOOD GLUCOSE LEVEL FOLLOWING EPINEPHRINE ADMINISTRATION IN NEWBORN INFANTS

AGE GROUP AND ROUTE OF EPINEPHRINE ADMINISTRATION *	NO. OF CASES	TIME OF PEAK RISE IN BLOOD GLUCOSE LEVEL											
		30 MIN.		1 HOUR		1½ HOURS		2 HOURS		2½ HOURS		3 HOURS	
		NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL
Birth to 24 hours													
Epin. subcut.	12	2	16.7	2	16.7	3	25	3	25	0	0	2	16.7
Epin. I.M.	14	0	0	2	14.3	1	7	7	50	4	28.6	0	0
24-48 hours													
Epin. subcut.	6	0	0	1	16.7	2	33.4	3	50	0	0	0	0
Epin. I.M.	7	0	0	0	0	1	14.3	5	71.5	0	0	1	14.3
48-96 hours													
Epin. subcut.	10	0	0	2	20	3	30	4	40	0	0	1	10
Epin. I.M.	6	0	0	1	16.6	3	50	2	33.3	0	0	0	0
5-10 days													
Epin. subcut.	5	1	20	3	60	1	20	0	0	0	0	0	0
Epin. I.M.	3	0	0	2	66.7	1	33.3	0	0	0	0	0	0

*Epin. subcut. = epinephrine subcutaneously; Epin. I.M. = epinephrine intramuscularly.

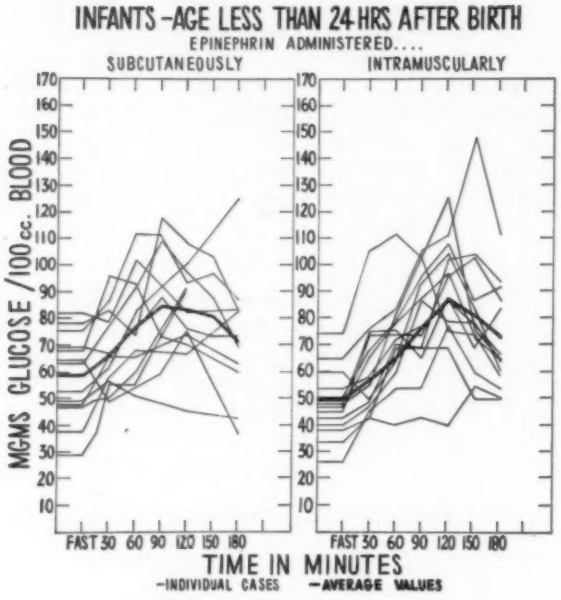

Chart I.

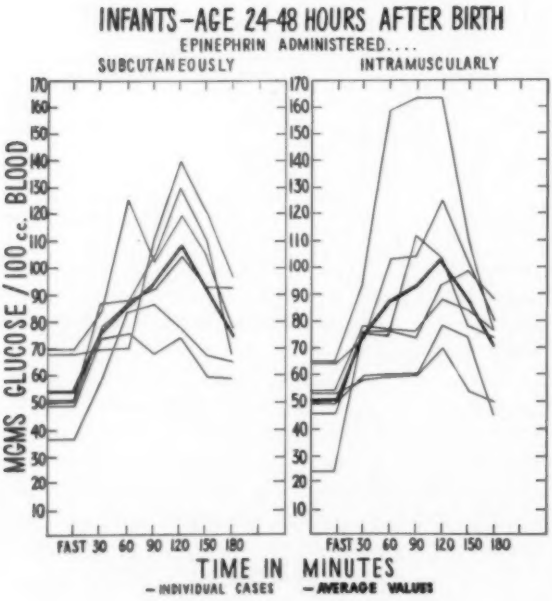

Chart II.

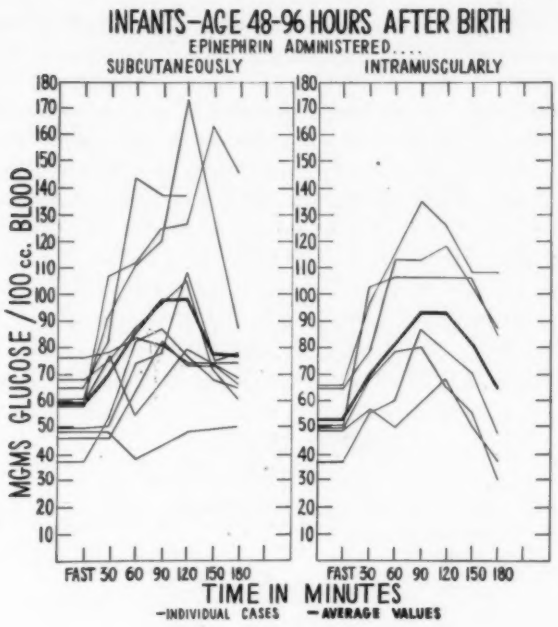

Chart III.

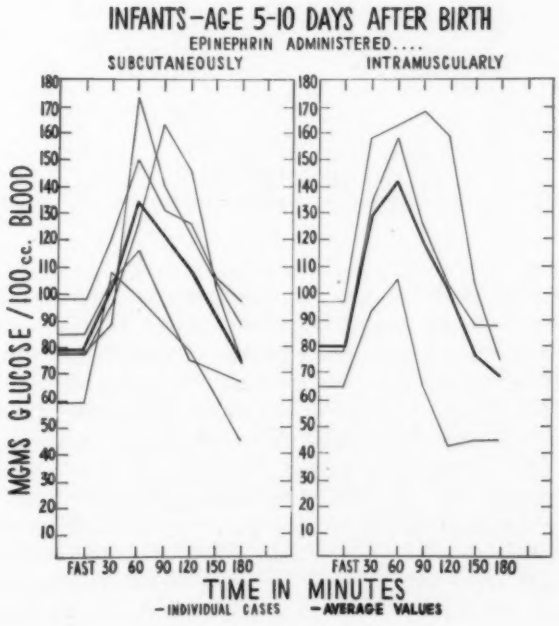

Chart IV.

The route of administration is a factor of importance in the extent of response to epinephrine only in the group of infants less than 24 hours of age. Early in our study it was noted that blanching at the site of subcutaneous injection of epinephrine was of longer duration in infants newly born than in older infants, even though the end point was not at all sharp. The blanching lasted as long as two to three hours in some instances. To eliminate the factor of difference in rate of absorption, the drug was administered thereafter to alternate infants subcutaneously and intramuscularly. The data summarized in Table I show that infants on their first day of life, have a smaller glycemic response (37 mg. per 100 ml. blood) to the subcutaneous administration of epinephrine than do infants given the drug by intramuscular injection (mean 51 mg. per 100 ml. blood). After the first twenty-four hours of life, the mode of administration made no apparent difference in the height of rise in glucose level.

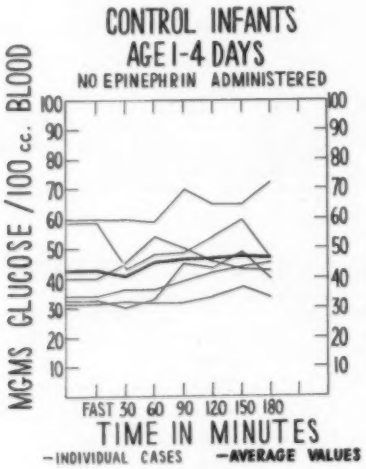

Chart V.

One finding appears to be clear cut: the shape of the epinephrine tolerance curve varies with the age of the infant (Table II). A different type of curve is noted in the younger infant groups (Charts I, II). In these, the rise and fall of blood glucose takes place more slowly, so that the peak rise occurs frequently between one and one-half to two hours after epinephrine injection, and at the end of the three-hour period the blood glucose level has not yet returned to fasting level. This is in marked contrast to the sharp rise and fall of the curves obtained in the 5- to 10-day-old infant (Chart IV). In this group the peak rise usually occurs at one hour with a return to fasting level at two to two and one-half hours. Infants in the age range of 48 to 96 hours (Chart III) have curves of both types with average curves of an intermediate nature. The average curves of the 5- to 10-day-old group compare favorably with those

reported by Livingston and Bridge[8] using the same epinephrine dosage on a group of infants ranging in age between 3 and 22 months.

To study the effect of age on the epinephrine tolerance curve, epinephrine was administered twice to the same infant in seven instances. It would have been ideal had it been possible to study all of the infants in this manner. Unfortunately, the majority of full-term infants in the group under survey were discharged from the hospital on the third or fourth day after birth. The epinephrine tolerance curves obtained in the same infant at different ages are shown in Table III. Again the fasting level tends to be lower at the younger age. The difference in timing of peak rise and fall is again evident, the maximum rise occurring earlier in the older infant. The wide variation which seems to characterize the degree of response of individual infants to epinephrine may be noted by comparison of the curves obtained in infants O. N. and C. A. The height of the curve obtained from the same infant at different ages tends to run somewhat parallel in the few cases studied in this manner.

TABLE III. BLOOD GLUCOSE LEVELS FOLLOWING EPINEPHRINE ADMINISTRATION IN THE SAME INFANT AT DIFFERENT AGES

CASE	ROUTE OF EPINEPHRINE ADMINISTRATION*	AGE OF INFANT	LEVEL OF BLOOD GLUCOSE IN PERIOD FOLLOWING EPINEPHRINE ADMINISTRATION						
			FASTING	30 MIN.	1 HOUR	1½ HOURS	2 HOURS	2½ HOURS	3 HOURS
(1) A. L.	Subcut.	5 hr.	68	67	76	87†	70	69	68
		3 da.	76	76	84†	81	74	—	72
(2) C. L.	I.M.	5 hr.	40	57	60	87†	79	78	64
		3 da.	50	68	78	80†	64	54	50
(3) G. A.	I.M.	11 hr.	43	49	70	70	102	104†	94
		3 da.	65	78	106	106	115†	100	95
(4) H. U.	Subcut.	10 hr.	38	58	68	—	57	—	82†
		3 da.	61	78	103†	—	79	—	68
(5) H. S.	Subcut.	9 hr.	49	66	66	—	74†	—	64
		7 da.	84	103	115†	—	74	—	64
(6) O. N.	I.M.	39 hr.	54	78	76	76	88†	84	76
		7 da.	65	93	105†	65	43	45	45
(7) C. A.	I.M.	48 hr.	64	92	158	163†	163	111	78
		7 da.	78	133	158†	125	103	88	88

*Subcut. = epinephrine subcutaneously; I.M. = epinephrine intramuscularly.
†Peak rise.

Side effects of epinephrine were not studied to any great extent in the present investigation. No conclusions could be drawn from a study of heart rate after epinephrine administration. The rate tended to become more rapid, but that of control infants of the same age showed as wide a fluctuation. This effect is now being studied in greater detail. Two interesting side effects of epinephrine administration, however, were evident. It was noted that infants of 2 days of age and older, who were irritable and crying after the seven-hour fast, frequently became quiet and went to sleep after receiving epinephrine. Such an observation could be explained, perhaps, by increase in blood sugar level with correction of the hypoglycemia. Likewise, in the oldest group (5 to 10 days of age) the infants were noted frequently to be irritable and crying again at the end of the three-hour test period. A good rise in blood glucose could often be predicted by the infant's behavior.

The well-recognized effect of epinephrine in increasing blood coagulation was evident throughout the study. The taking of blood specimens was discontinued in some infants because of difficulty in obtaining adequate blood samples before the occurrence of clotting. It was felt that repeated puncture would not give valid results since crying, excessive muscular activity, and similar reactions might in themselves increase blood sugar levels through sympathetic stimulation.

Because of the marked variation of glycemic response to epinephrine encountered in individual newborn infants, the epinephrine tolerance test apparently cannot be considered a reliable test of liver function during the first week of life.

DISCUSSION

The results obtained in this study indicate that, although infants have a low blood glucose level, they are capable of responding to epinephrine with a rise in blood glucose. This finding is in agreement with the belief of earlier workers that hypoglycemia of the newborn period is not attributable to poor stores of liver glycogen.[1-6]

The shape of the epinephrine glucose tolerance curve changes with increasing age after birth. The slow rise and fall of blood glucose level in the early days of life is in sharp contrast to that seen in infants older than one week. While the cause of this peculiar glycemic response shown by newborn infants is not clear, several explanations for the phenomenon are possible:

1. Differences in the capacity of the infant for the handling of epinephrine.
2. Differences in rate of glycogenolysis and glycogenesis.
3. Stimulation by epinephrine of other endocrine glands, notably the adrenal cortex and anterior pituitary.

The breakdown of epinephrine has not been studied in infant subjects. The slow and prolonged rise in blood glucose following its injection may be due to slower absorption or slower oxidation of the drug, or a combination of both these factors. An attempt was made to exclude the factor of slower absorption by the administration of epinephrine by both subcutaneous and intramuscular routes. After the first day of life the maximal response was similar in both groups, so that no difference could be ascribed to slow absorption.

The possibility that epinephrine may be metabolized more slowly in early life cannot be disregarded. In vivo, injected epinephrine is believed to be broken down rapidly by enzymatic oxidation in the tissues.[9] In vitro, it is slowly oxidized in blood and tissue fluids. Reducing agents such as amino acids and ascorbic acid, present in blood and tissue fluids, are considered responsible for this retarded oxidation. In this connection it is interesting to speculate on possible effects of the high ascorbic acid level of the newborn infant and the defect in metabolism of tyrosine and phenylalanine shown by Levine[12] to be characteristic of premature infants aged 13 to 47 days. Epinephrine and tyrosine are closely related in chemical structure, and it may be that tyrosine is associated in some way with the synthesis of epinephrine.

The reactions involved in glycogenolysis and glycogenesis may proceed at a slower rate in newborn infants. However, so far as the present authors are aware, there has been no experimental work to support such an explanation.

The third possibility is that injected epinephrine mediates the action of some other endocrine gland, particularly the adrenal cortex or anterior pituitary. Recent experimental work has linked the adrenal medulla, anterior pituitary, and adrenal cortex.[13, 14] It is believed that epinephrine plays a part in the control of adrenal cortical activity, the control being mediated through release of adrenocorticotrophic hormone from the anterior pituitary. Perhaps the slow rise of blood glucose and its slow fall seen in the epinephrine tolerance curve of early life, may be explained by a stimulating action of epinephrine on the adrenal cortex or anterior pituitary. Such a stimulus could bring about a prolonged rise in blood sugar independent of the amount of liver glycogen immediately available. This possibility may be a serious consideration if epinephrine proves to be absorbed and metabolized as rapidly in newborn infants as it is in the experimental animal.

The first week of life is characterized by rapid and profound changes in endocrine balance before the infant reaches a new balance characteristic of postnatal life.[15] What influence maternal hormones exert on the anterior pituitary and through it on the adrenal cortex and thyroid, has not yet been evaluated adequately. However, it is possible that a transient depression of pituitary function with secondary hypofunction of the thyroid and adrenal cortex may occur during the first week of life. The timing of the high estrogen level, low basal metabolic rate, and low glucocorticosteroid excretion of the neonatal period[16] is highly suggestive of primary pituitary involvement.

The explanation for the progressive change in shape of the epinephrine tolerance curve during the first ten days of life is not clear at present. Perhaps the answer may be forthcoming when more is known concerning endocrine relationships and liver enzyme relationships in the neonatal period.

CONCLUSIONS

The response of the blood glucose level to epinephrine administration was studied in sixty-three healthy, full-term newborn infants ranging from 4 hours to 10 days of age. These infants were divided into groups according to age and route of epinephrine administration (intramuscularly or subcutaneously). Six infants varying in age from 1 to 4 days were subjected to the same procedures with the one exception that no epinephrine was given.

1. All values obtained were extremely variable: fasting blood glucose levels, height of peak rise, time of peak rise, and time of return to fasting level. However, the great majority of infants showed a definite rise in blood glucose subsequent to epinephrine administration. The degree of rise showed no constant relationship to the fasting level.

2. Infants less than 24 hours of age given epinephrine subcutaneously, showed a lower rise in blood glucose than similar infants given the drug intramuscularly. After 24 hours of age, the response was similar in both groups.

3. All infants, 1 to 5 days of age showed comparable rises in blood glucose. The 5- to 10-day-old group showed a higher rise similar to that obtained by Livingston and Bridge in older infants (3 to 22 months of age).

4. In younger infants the rise in blood glucose and return to fasting level were delayed. As the infant approached the end of the first week of life, the curves approximated more closely those found in older infants.

5. In seven instances the infants were studied a second time, the same procedures being followed at a later age. The main difference noted with increasing age was a higher fasting level and a more rapid rise and fall in the older infant.

6. The possible significance of these findings in relation to changes occurring after birth is discussed.

7. The glycemic response to epinephrine is too variable for utilization as a test of liver function in newborn infants.

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REFERENCES

1. van Crevald, S.: Carbohydrate Metabolism of Premature Infants, Am J. Dis. Child. **38:** 912, 1929.
2. Hartmann, A. F., and Jaudon, J. C.: Hypoglycemia, J. PEDIAT. **11:** 1, 1937.
3. Norval, M. A., Kennedy, R. L. J., and Berkson, J.: Blood Sugar Values in Newborn Infants, J. PEDIAT. **34:** 342, 1949.
4. Norval, M. A.: Blood Sugar Values in Premature Infants, J. PEDIAT. **36:** 177, 1950.
5. Windle, F. W.: The Physiology of the Fetus, Philadelphia, 1940, W. B. Saunders Company, pp. 210-215.
6. Van Crevald, S.: Glycogen Disease, Medicine **18:** 1, 1939.
7. Lauber, F. V., and Mattice, M. R.: Microdetermination of Blood Glucose, J. Lab. & Clin. Med. **29:** 113, 1944.
8. Livingston, S., and Bridge, E. M.: Tests of Carbohydrate Metabolism in Infants, J. A. M. A. **119:** 117, 1942.
9. Best, C. H., and Taylor, N. G.: The Physiological Basis of Medical Practice, Baltimore, 1945, Williams & Wilkins Company, pp. 685-692.
10. Sollman, T.: A Manual of Pharmacology, Philadelphia, 1948, W. B. Saunders Company, pp. 685-692.
11. Manahan, C. P., and Eastman, N. J.: Cevitamic Acid Content of Fetal Blood, Bull. Johns Hopkins Hosp. **62:** 478, 1938.
12. Levine, S. Z., Marples, E., and Gorden, H. H.: Defect in Metabolism of Tyrosine and Phenylalanine in Premature Infants, J. Clin. Investigation **20:** 209, 1941.
13. Vogt, M.: Cortical Lipids of the Normal and Denervated Suprarenal Gland Under Conditions of Stress, J. Physiol. **106:** 394, 1947.
14. Long, C. N. H.: Recent Studies on the Function of the Adrenal Cortex, Bull. New York Acad. Med. **26:** 260, 1947.
15. Smith, C. A.: The Physiology of the Newborn Infant, Springfield, Ill., 1946, Charles C Thomas, Publisher.
16. Venning, E. H., Randall, J. P., and Gyorgy, P.: Excretion of Glucocorticosteroids in the Newborn, Endocrinology **45:** 430, 1949.

A NOTE ON THE TREATMENT OF DIAPER RASH WITH ALKYL-DIMETHYL-BENZYL-AMMONIUM CHLORIDES (ROCCAL)

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IT HAS BEEN recognized for some time that certain inflammatory rashes of the diaper area are regularly accompanied by an odor of ammonia, especially if the wet diapers remain unchanged for several hours. Although the causal relationship of ammonia to this rash was assumed, Cooke[1] was the first to point out that the ammonia was produced by urea-splitting organisms normally present in the stools of these infants, particularly *Bacterium ammoniagenes*. This concept naturally led to the use of a residual antiseptic in the diaper to destroy the urea-splitting organism, or at least inhibit its metabolism.

Biehloride of mercury was one of the earliest to be used, and was quite effective, although it has the obvious disadvantage of being too toxic for common household use. Boric acid solution has been, and still is, a popular method of diaper impregnation. Most recently para di-isobutyl-cresoxy-ethoxy-ethyl dimethyl benzyl ammonium chloride monohydrate (Diaparene) has been introduced by Benson and co-workers[2] and found effective.

An alternative, indirect method of treatment has been the application of a protective coating to the skin, such as zinc oxide or boric acid ointment. In the mild cases this is found to permit healing, although irritation may begin again after treatment has stopped. The most severe rashes are least likely to respond to this form of therapy; the mild rashes frequently respond to almost any form of treatment which involves an improvement in local hygiene. In many cases, once the skin has returned to normal, it is usual for a rash-free period of weeks or months to follow, even though the causative organisms may still be present, and even though ammoniacal odors may persist; other cases will regularly show a recurrence after treatment is stopped.

The ideal treatment for ammoniacal dermatitis (and, presumably, the ideal prophylaxis) would seem to involve impregnating the diaper with some nontoxic, nonirritating substance capable of inhibiting ammonia formation. The substance used should be cheap, easily available, and easy to prepare for use. A mixture of high molecular weight alkyl-dimethyl-benzyl-ammonium chlorides has been commercially available for some time under the name Roccal.* It has been used extensively for disinfection and sanitization. It is easily available and of relatively low cost. The present study was undertaken to evaluate the use of Roccal in the treatment and prevention of diaper rashes.

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*Roccal is distributed by Sterwin Chemicals, Inc., and by Winthrop-Stearns, Inc. It contains 10 per cent active alkyl-dimethyl-benzyl-ammonium chlorides.

Bacteriologic Studies.—The antibacterial activity of Roccal was tested against Proteus OX_2, a standard organism with known urea-splitting activity. By the tube method, as indicated in Table I, complete inhibition of growth was observed after 10 minutes' exposure to a solution of Roccal diluted 1:30,000; after 5 minutes' exposure a 1:20,000 dilution was required.

TABLE I. ROCCAL STUDIES BY THE TUBE METHOD: EFFECT OF ROCCAL ON PROTEUS OX_2

DILUTIONS OF ROCCAL	BROTH CULTURES TAKEN AFTER EXPOSURE FOR	
	5 MINUTES	10 MINUTES
1:1,000	No growth	No growth
1:5,000	No growth	No growth
1:10,000	No growth	No growth
1:20,000	No growth	No growth
1:30,000	Growth	No growth
1:40,000	Growth	Growth
1:50,000	Growth	Growth
1:100,000	Growth	Growth
Controls: #1 Roccal (undiluted) and culture	No growth	No growth
#2 H_2O and culture	Growth	Growth

(0.5 c.c. of a 24° C. culture of Proteus OX_2 was transferred to 5 c.c. of the appropriate dilution of Roccal. After five- and ten-minute exposure a loopful of the mixture was planted in 5 c.c. of broth.)

Using a saline suspension of normal infant stool as the test inoculum, the tube method showed a complete inhibition of growth after exposure for 10 minutes to a 1:20,000 dilution of Roccal (Table II).

TABLE II. ROCCAL STUDIES BY THE TUBE METHOD: EFFECT OF ROCCAL ON STOOL SUSPENSION IN BROTH

DILUTIONS OF ROCCAL	BROTH CULTURES MADE AFTER EXPOSURE FOR	
	5 MINUTES	10 MINUTES
1:1,000	No growth	No growth
1:5,000	No growth	No growth
1:10,000	No growth	No growth
1:20,000	No growth	No growth
1:30,000	Growth	Growth
1:50,000	Growth	Growth
Controls: #1 Roccal (undiluted) and culture	No growth	No growth
#2 H_2O and culture	Growth	Growth

Original stool suspension made from fresh stool of healthy young infant, was incubated for 24 hours. Then 0.5 c.c. was transferred to 5 c.c. of the indicated dilution of Roccal and, after appropriate time, a loop of that mixture was placed in tryptophane broth incubated 24 and 48 hours, with results as tabulated.

By the cup method, using a 15 mm. porous cup, a zone of inhibition of the growth of Proteus OX_2 was produced by Roccal at a dilution of 1:5,000, but no inhibition using a dilution of 1:10,000. When a saline suspension of normal infant stool was used as the inoculum, inhibition was found with Roccal diluted 1:1,000, but not with a dilution of 1:5,000.

The tube method is reputedly more accurate, and certainly gives a closer approximation to the conditions obtaining in the diaper than the cup method. On the basis of these tests, a solution of Roccal diluted 1:5,000 was selected as of more than adequate strength for inhibiting ammonia formation in the diaper.

Since the active substance is present in standard strength Roccal as commercially available in a 10 per cent solution, a 1:5,000 dilution results from diluting one part of the commercial preparation with 500 parts of water. The dilution of Roccal used for rinsing the diapers is of course only an approximation of the final dilution in the diapers since the volume of urine in which the Roccal redissolves is a variable.

Skin Testing.—Skin testing previous to the use of Roccal therapeutically was carried out by applying a 2 inch × 2 inch gauze patch moistened with a 1:1,000 dilution of Roccal to the backs of 100 infants aged 1 day to 2 years. The patch was left in contact with the skin for twenty-four hours. No reactions of any kind were noted either at the end of the twenty-four hour period or after forty-eight hours. No irritation was noted in any of the 145 patients in whom Roccal was used therapeutically or prophylactically.

Diagnosis.—The mildest form of ammoniacal dermatitis is an erythema of all or part of the diaper area. Further progression of the lesion leads to blistering, crusting, and ulceration. When the rash has persisted for several weeks or months, it assumes a chronic character with indolent ulcers having indurated borders, dark red papules, and, if general hygiene is poor, pustules. Healing is accompanied by transient brown pigmentation and in the most severe cases, by scarring. A special characteristic in circumcized male infants is the formation of superficial ulcers with crusting about the urinary meatus and over the glans penis. This may be the only manifestation of ammoniacal dermatitis. It usually gives symptoms of severe pain and bleeding on urination, and sometimes produces urinary retention because of the pain on voiding.

In the present series, the diagnosis has been restricted to patients displaying a typical rash restricted to the diaper area, without diarrhea and without evidence of other disease. The majority of the mothers spontaneously offered the information that the diapers smelled of ammonia. No infant was included who had had any response to another method of treatment although in the majority other therapy had been unsuccessful. All patients treated were seen at the Children's Medical Center Out-Patient Department and in the offices of staff members of the Children's Medical Center. No in-patients were included.

Methods.—All patients were treated in the same fashion. The mothers were instructed to use no other medication such as antiseptic powders, ointments, or diaper rinses. The diapers were washed and rinsed as usual, using a good nonionic synthetic detergent instead of soap, which reduces the bactericidal power of Roccal and of all similar antiseptics. Immediately before drying, the diapers were given a final rinse in Roccal solution, prepared in a dilution of 1:5,000 (1 teaspoonful of 10 per cent Roccal to 2 quarts of tap water), wrung out, and hung up to dry. Diapers prepared in this way were indistinguishable from diapers prepared without Roccal in color, softness, and odor.

RESULTS

Prophylaxis.—An attempt was made to prevent diaper rashes in a group of ninety incontinent, nonambulatory infants and children in a state mental

institution.* These patients were kept in two pairs of wards, each of the pairs being comparable to the other in numbers, types of patients, and amount of nursing care available. The patients were all infants with an easily recognizable defect, such as mongolism or microcephaly, or older children with obvious severe motor and mental retardation.

The diapers were cleaned by commercial laundry methods, and were the same for each of the four wards, with the exception that Roccal solution 1:5,000 was used as the final rinse in the diapers used in one ward of each pair. The other two wards served as control groups.

Even before the test period about 10 per cent of the infants and 50 per cent of the older children had various lesions of the buttocks ranging from mild erythema to severe ulceration and chronic infection. For a period of three months Roccal was used in the diapers of the test group, and examinations of the patients in both test and control groups were made twice weekly.

No significant changes in the existing lesions were noted in either group over the three-month period. In both groups, many patients at one time or another had transitory periods of erythema, some with inflammatory maculopapules, but there did not appear to be any difference between the prophylactically treated and the control groups. At no time in either group, however, did there appear the typical blistered or acutely ulcerated rash of ammoniacal dermatitis.

It seems likely that most of the rashes in these patients were due to nonspecific irritation and the nutritional and hygienic difficulties incidental to gross mental defects. The conditions of this trial are certainly not applicable to the prevention of diaper rashes in normal infants. Of the cases to be discussed below, in which diaper rash was treated by Roccal, eight recurred after cessation of therapy. In each case reinstitution of Roccal therapy was again effective, and the effect was evident as long as the treatment was continued. It appears that in these cases at least, Roccal would have been effective in preventing the rash completely. The use of Roccal to prevent recurrence was continued for one month in one case without harmful effects. For these reasons, it is felt that the use of Roccal to prevent diaper rashes in normal children in usual circumstances would be successful.

Treatment.—Roccal impregnated diapers were used in the treatment of 64 infants with diaper rash as listed in Table III. Nineteen of these were mild and all were cleared in less than one week of therapy, most in less than five days. There were 28 cases considered moderate, all with acute inflammation and ulceration; 25 of these were completely clear at the end of one week, 2 cleared after two weeks, and 1 failed to respond. Sixteen cases were considered severe, and showed ulcers with indurated margins, thick maculopapules and some pustulation. Most of the severe cases were also chronic. Healing in the severe cases was difficult to evaluate since pigmentation, healing of deep ulcers, and scarring all tended to persist after the rash was quiescent. In the 16 severe cases, however, inflammatory changes were gone after one week in 12 cases, after two weeks in 3 cases; there was no response in one case.

*The authors are indebted to Dr. Karl V. Quinn of Wrentham State Hospital, Wrentham, Massachusetts, for his permission to treat these patients.

TABLE III.

CASE NO.	NAME	AGE (MO.)	SEX	SEVERITY*	DAYS OF TREATMENT TO CURE	REMARKS
1	A. C.	4	M	Mild	5	Meatitis alone
2	C. G.	11	M	Mild	2	Meatitis alone
3	M. T.	16	M	Mild	5	Meatitis alone
4	B. K.	7	M	Mild	3	
5	M. D.	10	M	Mild	7	
6	R. D.	6	M	Mild	5	
7	D. H.	14	F	Mild	6	
8	E. H.	14	M	Mild	6	
9	M. H.	5	F	Mild	2	
10	R. K.	2	M	Mild	6	
11	T. K.	8	M	Mild	5	
12	D. A.	5	M	Mild	4	
13	D. T.	7	M	Mild	2	
14	C. M.	6	F	Mild	5	
15	T. C.	14	M	Mild	5	
16	D. J.	5	F	Mild	6	
17	S. H.	2	F	Mild	7	
18	S. B.	8	F	Mild	7	
19	L. G.	14	F	Mild	4	
20	M. M.	5	M	Mod.	7	
21	D. D.	2	M	Mod.	5	
22	M. R.	8	M	Mod.	3	
23	E. C.	9	M	Mod.	5	
24	T. R.	6	M	Mod.	4	
25	E. L.	5	F	Mod.	3	
26	R. O.	24	F	Mod.	7	
27	D. O.	3	M	Mod.	6	
28	H. V.	14	M	Mod.	6	
29	P. D.	4	M	Mod.	7	
30	W. K.	24	M	Mod.	6	
31	C. M.	7	M	Mod.	6	
32	N. C.	7	M	Mod.	6	
33	L. B.	7	M	Mod.	7	
34	J. R.	3	M	Mod.	7	
35	R. P.	10	M	Mod.	4	
36	D. N.	5	M	Mod.	3	
37	B. C.	5	M	Mod.	No response	
38	C. Y.	8	M	Mod.	7	
39	C. B.	7	F	Mod.	7	
40	F. W.	5	F	Mod.	5	
41	F. G.	6	M	Mod.	4	
42	N. G.	17	F	Mod.	7	
43	P. B.	2	M	Mod.	7	
44	D. H.	16	F	Mod.	10	Improved after 1 day
45	S. H.	2	F	Mod.	14	Improved after 7 days
46	L. C.	2	M	Mod.	7	
47	C. A.	5	M	Mod.	7	
48	T. G.	16	M	Mod.	--	
49	J. W.	1	F	Sev.	7†	
50	D. T.	1	M	Sev.	7	Accompanied by severely ulcerated penis
51	L. R.	4	F	Sev.	14	
52	J. V.	18	F	Sev.	3	
53	E. C.	8	M	Sev.	7	
54	B. C.	8	M	Sev.	7	
55	M. B.	10	F	Sev.	4	
56	E. C.	9	M	Sev.	7	
57	L. S.	6	M	Sev.	7	
58	E. W.	15	M	Sev.	No effect	Subsided with another commercial preparation
59	I. R.	11	F	Sev.	7	Rash of 3 months' duration before treatment
60	F. H.	13	F	Sev.	6	
61	M. M.	1½	M	Sev.	7	
62	S. B.	11	M	Sev.	10	
63	S. K.	6	M	Sev.	14	Rash present for 5 months
64	C. B.	8	M	Sev.	7	

*Mod. = moderate; sev. = severe.

†In severe cases macular brown pigmentation, healing ulcers, and scarring persisted for a variable time after all inflammation had subsided. The time of cure in the severe cases has has been judged by the clearing of all active inflammatory lesions.

DISCUSSION

The results in 62 of the 64 cases were good, with the time for clearing depending on the severity of the lesions present. The mild and moderate cases regularly were healed after one week of therapy. Chronic rashes with deep ulcers and pigmentation consistently began to improve within a few days, and inflammatory changes were gone within two weeks, usually within one.

Two cases failed to respond. It seems probable that in one of these other factors interfered with adequate treatment. No explanation can be given for the other failure, which subsequently cleared with another commercially available preparation. On the other hand, two cases responding to Roccal had previously failed to respond to another preparation.

It should be repeated that the mildest cases respond fairly well to bland ointments and more frequent changes of the diaper. In these cases boric acid ointment and better hygiene will be rapidly curative. When these simple measures prove ineffective, or in any patient with ulceration or severe erythema when first seen, a residual antiseptic in the diaper provides logical treatment. Roccal has proved highly effective when used as an impregnating antiseptic in our hands and by comparison with other methods of treatment has the added advantage of cheapness and ease of use.

SUMMARY

1. A solution of alkyl-dimethyl-benzyl-ammonium chlorides (Roccal) has been effective in curing ammoniacal diaper dermatitis in 62 out of 64 cases, when used in a 1:5,000 dilution to impregnate the diaper after washing.

2. Reasons are presented for the belief that under usual circumstances Roccal would be equally effective for prophylaxis of this condition.

3. Roccal is nontoxic, nonirritating to the skin in recommended dilutions, is readily available and is of relatively low cost.

Gratitude is acknowledged to Mrs. Ann S. Buck for bacteriologic studies.

REFERENCES

1. Cooke, J. V.: The Etiology and Treatment of Ammonia Dermatitis of the Gluteal Region of Infants, Am. J. Dis. Child. **27**: 481, 1921.
2. Benson, Reuel A., Slobody, Lawrence B., Lillick, Lois, Maffia, Anthony, and Sullivan, Norbert: A New Treatment for Diaper Rash, J. PEDIAT. **31**: 369-374, 1947.

MEASURE OF IMMUNOLOGIC RESPONSES TO AN IMPROVED PREPARATION OF DIPHTHERIA AND TETANUS TOXOIDS (ALUM PRECIPITATED) COMBINED WITH PERTUSSIS VACCINE

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THE USE of combined vaccines and toxoids for active immunization, first suggested by Ramon,[1] has been generally accepted to be practical and effective. (A mixture of alum precipitated diphtheria toxoid and pertussis vaccine in no way interferes with the antigenicity of either component.[2] According to a number of investigators[3, 4, 5] diphtheria and tetanus toxoids combined with *Hemophilus Pertussis* vaccine have produced satisfactory immunity responses.

We have used combinations of *H. pertussis* vaccine with diphtheria and tetanus toxoids for simultaneous immunization in all infants coming to the Well Baby Clinic at St. Christopher's Hospital for Children. Progressive improvements in such combinations have been observed and followed with interest.

An improved preparation of *H. pertussis* vaccine with alum precipitated diphtheria and tetanus toxoids was made available for clinical trial.† The combination was standardized so that one complete immunization treatment consisted of three 0.5 c.c. injections totaling two human doses each of diphtheria and tetanus toxoids and 45,000 million *H. pertussis* organisms. The preparation was said to contain considerably less than 10 mg. of alum per dose.

It has been our custom, and we followed it in this study, to give three injections of a preparation of *H. pertussis* and diphtheria and tetanus toxoids (alum precipitated) to all well babies at the age of 5 or 6 months. These deep intramuscular injections were given at monthly intervals into alternate buttocks. The syringes and needles were sterile and dry. Care was taken to keep the needle's surface free of the mixture, and great care was exercised to avoid injection into blood vessels.

The purpose of this study was to attempt an evaluation of the immunity response in 100 well babies. We selected every other baby of the first 50 babies for a comparative study of *H. pertussis* agglutinin titers and pertussis skin test; antitoxin titers and Schick test for diphtheria, and antitoxin titers for tetanus. This procedure gave us the immunity index as measured by circulating antibody-antitoxin titers and skin tests in 25 babies. In the remaining 75 babies the immunity index was measured by skin tests for *H. pertussis* and diphtheria.

H. Pertussis Immunity Response:—The agglutination titer of the blood serum has been suggested as an index of immunity.[6, 7] A skin test has also been

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†The diphtheria-tetanus toxoids (alum precipitated) combined with pertussis vaccine was supplied by the Medical Research Department of the National Drug Company, Philadelphia, Pa.

proposed for measuring the immunity or susceptibility to whooping cough.[8,9] Felton and Flosdorf[8] have shown that there is a close correlation between the agglutination titer and the positive skin test. Sauer and Markley,[10] following a comparative study of the pertussis agglutinogen skin test and the complement fixation test, concluded: "The agglutinogen skin test seems to be a simple method by which persons who are immune to pertussis can be readily differentiated from those nonimmune." Boines[11] and Maggio[12] confirmed these observations in later reports.

Blood samples were collected from 25 babies before skin test and immunization, and six months after immunization.

Pertussis skin tests were done in all of the babies before immunization and six months after immunization.

The results of the blood studies for *H. pertussis* agglutinin and of the skin tests are summarized in Table I.

TABLE I. *H. pertussis* Agglutination and Agglutinogen Tests

H. pertussis Agglutination Test									
		TITER							
GROUP I	BABIES	NEG.	20	40	80	160	320	640	1280
Before immunization	25	21	–	–	2	–	2	–	–
After immunization	25	1	1	3	3	5	3	6	3

H. pertussis Agglutinogen Skin Test			
GROUP	BABIES	POSITIVE IMMUNE	NEGATIVE IMMUNE
Group I			
Before immunization	25	0	25
After immunization	25	25	0
Group II			
Before immunization	75	1	74
After immunization	75	75	0

Discussion.—It was reported by Sako[13] that in young infants, antibody titer is reached in from two to four months after completion of immunizations, after which a plateau is maintained for three years or longer. Considering a titer of 1:320 or above as an index of positive immunity, Sako[13] got strong agglutinin titers in 50.55 per cent of his subjects. Our results in this group of 25 babies (48 per cent) are closely comparable. However, we did have four babies with agglutinins of low titer and whose *H. pertussis* agglutinogen skin tests were negative immune prior to immunization.

There is an apparent correlation between the *H. pertussis* immunity index as assayed by the agglutination tests and the skin test.

Diphtheria Immunity Response.—In 25 babies, diphtheria antitoxin levels were determined before and six months after immunization. In these babies the Schick test was also done before and after immunization.

In the remaining 75 babies the Schick test was performed before and after immunization. The results are summarized in Table II.

Discussion.—The level of diphtheria antitoxin which is considered as adequate is placed at 0.03 unit per cubic centimeter.[14] On this basis, the 18 babies tested before immunization did not have adequate protection. However, the Shick test in the 25 babies showed 40 per cent to be immune compared to

TABLE II

Diphtheria Antitoxin Levels

GROUP I	BABIES	UNITS PER CUBIC CENTIMETER							
		0.001	0.008	0.03	0.07	0.1	0.15	0.2	0.25
Before immunization	18*	16	2	–	–	–	–	–	–
After immunization	25†	–	–	1	1	3	4	11	2

Schick Tests

GROUP	Babies	POSITIVE	NEGATIVE
Group I			
Before immunization	25	15	10
After immunization	25	3	22
Group II			
Before immunization	75	59	16
After immunization	75	10	65

*Sufficient serum could not be obtained from seven babies for the diphtheria antitoxin level determination.

†One subject in this group showed a level of 0.4, another 0.55 unit per cubic centimeter, and one showed a level of 0.8 unit per cubic centimeter.

60 per cent nonimmune. Following immunization there were 88 per cent with an adequate immunity index compared to 12 per cent nonimmune as assayed by the Schick test. The diphtheria antitoxin levels after immunization were adequate in all 25 babies for protection.

The Schick tests in the group of 75 babies before immunization showed 78.66 per cent nonimmune and 21.33 per cent apparently immune. After immunization the results were 13.3 per cent nonimmune to 86.66 per cent apparently immune.

Percentage-wise, there is a very close correlation between the two groups in the Schick tests. Since all the babies in Group I showed adequate diphtheria antitoxin levels following immunization, we may assume that all 75 babies in Group II had adequate levels for protection.

Jensen[15] pointed out and stressed that the degree of correlation between the Schick reaction and level of antitoxin titer varies in different individuals. Subjects with negative Schick reactions may have a good potential immunity even when the amount of circulating antitoxin is low. We agree with Vohlquist and Hogstedt[16] that nonspecific individual differences of the skin may play a role which should not be neglected for the specific tissue factor.

Tetanus Immunity Response.—Tetanus antitoxin titrations were made in 25 babies before and six months after immunization with the combined *H. pertussis* vaccine, diphtheria and tetanus toxoids, alum precipitated. The results are summarized in Table III.

Discussion.—The amount of tetanus antitoxin in the blood necessary for adequate protection has not been definitely established. However, most authorities agree that 0.1 unit per cubic centimeter is protective.[17] In this series of babies, adequate protection was established for tetanus.

TABLE III. TETANUS ANTITOXIN LEVELS

	BABIES	UNITS PER CUBIC CENTIMETER
Before immunization, Sufficient serum from	22	0.0001 or less
After immunization, Sufficient serum from	23	0.2 or more

During the immunization of the entire series of 100 babies, over 300 injections of the *H. pertussis* vaccine combined with alum precipitated diphtheria and tetanus toxoids were given with no serious systemic or local reactions. The few temperature elevations and local reactions reported were slight and of short duration. A few nodules, small in size, remained after injections, but these eventually disappeared without treatment.

SUMMARY

1. In 25 babies a comparative study between *H. pertussis* agglutinins and the pertussis agglutinogen skin test was made before and six months following immunization with a combination of *H. pertussis* vaccine and alum precipitated diphtheria and tetanus toxoids.

2. Diphtheria antitoxin levels and Schick reactions were compared in a small group of babies.

3. Tetanus antitoxin blood levels were determined in a small group of babies before and after immunization.

4. Schick tests and *H. pertussis* agglutinogen skin tests were done in an additional 75 babies before and after immunization.

5. We observed an apparent correlation between the *H. pertussis* agglutination test and the agglutinogen skin test as a measure of immunity.

6. A variation in the correlation between diphtheria antitoxin titers and Schick reactions was noted. On the basis of the antitoxin titers all babies tested showed adequate protective levels. However, in this group 12 per cent were Schick positive.

7. Following immunization all babies tested for tetanus antitoxin levels showed adequate amounts for protection.

8. In 75 babies the *H. pertussis* agglutinogen test showed 74 to be negative immune and after immunization this group tested 100 per cent positive immune.

9. The Schick test in 75 babies before immunization was positive in 78.6 per cent and negative in 21.3 per cent. After immunization we had 86.6 per cent negative and 13.3 per cent positive reactions.

10. We observed no serious systemic or local reactions in the two series of babies treated. A significant observation was the relatively few nodules, small in size, which resulted from the injections and which disappeared in a short time without treatment.

COMMENTS

An improved combination of *Hemophilus pertussis* vaccine and alum precipitated diphtheria and tetanus toxoids used in this study produced adequate protection to all three components as measured by antitoxin titrations for diphtheria and tetanus, and agglutinins for *H. pertussis*.

The *H. pertussis* agglutinogen skin test is apparently adequate in differentiating immune and nonimmune subjects.

REFERENCES

1. Ramon, G., and Zoeller, C.: Les "vaccins associes" par union d'une anatoxine et d'un vaccin meroben (TAB) en par melanges D'anatoxines, Compt. rend. Soc. de biol. 94: 106, 1926.

2. Schutze, E.: Bacteriology at the Lister Institute, Lancet **2**: 172, 1940.
3. Lapin, J.: Combined Immunization of Infants Against Diphtheria, Tetanus, and Whooping Cough, Am. J. Dis. Child. **63**: 225-237, 1942.
4. Daughtry-Denmark, Leila: Whooping Cough Vaccine, Am. J. Dis. Child. **63**: 453-466, 1942.
5. Miller, J. J., Jr., and Saito, T. M.: Concurrent Immunization Against Tetanus, Diphtheria, and Pertussis, Comparison of Fluid and Alum Precipitated Toxoids, J. PEDIAT. **21**: 31-44, 1942.
6. Flosdorf, E. W., and Kimball, A. C.: Comparison of Various Physical Means of Liberation of Agglutinogen From H. pertussis in Phase I, J. Immunol. **39**: 287-295, 1940.
7. Miller, J. J., Jr., and Silverberg, R. J.: Agglutinative Reaction in Relation to Pertussis and to Prophylactic Vaccination Against Pertussis With Description of New Technique, J. Immunol. **37**: 207-221, 1939.
8. Felton, H. M., and Flosdorf, E. W.: Clinical Results With the Use of Agglutinogen From Phase I H. pertussis as Skin Test for Susceptibility to Whooping Cough, J. PEDIAT. **22**: 259-264, 1943.
9. Flosdorf, E. W., Felton, H. M., Bondi, A., Jr., and McGuinness, A. C.: Intradermal Test for Susceptibility To and Immunization Against Whooping Cough Using Agglutinogen From Phase I H. pertussis, Am. J. M. Sc. **206**: 422-425, 1943.
10. Sauer, L. W., and Markley, E. D.: Whooping Cough: Pertussis Agglutinogen Skin Test After Immunization With H. pertussis vaccine, J. A. M. A. **131**: 967-969, 1946.
11. Boines, G. J.: A Skin Test to Measure Susceptibility to Whooping Cough, Delaware State M. J. **19**: 29-30, 1947.
12. Maggio, G. A.: Evaluation of Immunity to Whooping Cough, J. M. Soc. New Jersey **45**: 239-240, 1948.
13. Sako, W.: Studies on Pertussis Immunization, J. PEDIAT. **30**: 29-40, 1947.
14. Ratner, B.: Allergy-Anaphylaxis and Immunotherapy, Baltimore, 1942, Williams & Wilkins Company.
15. Jensen, C.: Immunisation antidiphtérique des enfants par une injection unique d'anatoxine antidiphtérique purifiée et concentrée, Compt. rend. Soc. de biol. **108**: 528-532, 1931.
16. Vohlquist, B., and Hogstedt, C.: Skin Factors in Schick Reaction, J. Immunol. **62**: 257, 1949.
17. Edsall, G.: Medical Progress, Active Immunization, New England J. Med. **235**: 256, 1946; **235**: 298, 1946; **235**: 328, 1946.

PREMATURE MORTALITY

An Analysis of 518 Cases of Prematurity With a Comparison of Nergo and White Races

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THE PURPOSE of this paper is to present our mortality in 518 premature infants born at Kings County Hospital during the months from January through December, 1949. We have presented a brief comparison of white and Negro premature babies.

The American Academy of Pediatrics has adopted the following definition of prematurity: "A premature infant is one who weighs 2,500 grams or less at birth (not at admission) regardless of the period of gestation. All live-born premature infants should be included, evidence of life being heart beating or breathing."[1] Anderson, Brown, and Lyon suggest that the gestation period for the Negro infant may actually be shorter than for the white infant. In a later study these authors presented data for lowering the upper limit of birth weight for prematurity from 2,500 to 2,350 grams for the Negro infants.[2]

INCIDENCE

In our analysis of the incidence of prematurity among 3,872 white and Negro patients we found that under the present definition of prematurity 20 per cent Negro and 15.5 per cent white babies were premature. Chart I shows the proportion of Negro to white patients including full-term and premature babies. If, however, we accept 2,350 grams as the upper limit for Negro babies, the incidence of prematurity for that race falls to 15.2 per cent. That would equalize the incidence of prematurity for both races. At Kings County Hospital the patients, whether Negro or white, have similar environmental and economic backgrounds. Approximately two-thirds of the obstetric patients attend prenatal clinic. The majority of patients with positive Wassermann tests have prenatal antisyphilitic therapy. In this brief survey we have not considered maternal illnesses and their influence on prematurity. Our findings support those of Anderson, Brown, and Lyon which justify the redefinition of prematurity for Negro babies to those weighing 2,350 grams or less at birth. We agree with their feeling that the two racial groups would be more nearly comparable under this new criterion. Their incidence of prematurity was 9 per cent for both races under the new standards.[2]

On Chart II we have divided the premature infants into four weight groups for comparison of mortality between the two races. We have added a table with the new standard for Negro premature infants for comparison with the old. The four weight groups for the new proposed standard are: (1) those

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CHART I. BIRTH STATISTICS AT KINGS COUNTY HOSPITAL, 1949

MONTH 1949	TOTAL	NEGRO FULL-TERM	WHITE FULL-TERM	NEGRO PREMATURE	WHITE PREMATURE
January	342	183	104	46	9
February	305	190	60	37	18
March	350	191	108	37	14
April	306	174	80	41	11
May	317	186	80	33	18
June	338	196	88	40	14
July	354	183	113	48	10
August	345	192	102	39	12
September	273	152	81	28	12
October	321	183	81	43	14
November	308	190	71	32	15
December	313	206	67	26	14
Total	3,872	2,226	1,035	450	161

Stillbirths: Negro premature 66
White premature 27
Incidence of Prematurity: Negro—20%
White—15.5%

CHART II. MORTALITY COMPARISON IN WEIGHT GROUPS

WEIGHT (GM.)	<1,000	1,000-1,500	1,500-2,000	2,000-2,500
White				
Premature infants	11	20	23	76
Deaths	10	8	5	0
Mortality	90%	40%	21.5%	0%
Negro				
Premature infants	29	25	81	254
Deaths	25	8	9	1
Mortality	86.2%	32%	11.1%	0.3%
WEIGHT (GM.)	<850	850-1,350	1,350-1,850	1,850-2,350
Negro				
Prematures	20	18	57	182
Deaths	18	11	9	4
Mortality	90%	61.1%	15.7%	2.1%

weighing less than 850 grams, (2) 850 to 1,350 grams, (3) 1,350 to 1,850 grams, and (4) 1,850 to 2,350 grams. Our aim is toward a more accurate comparison of mortality in different weight ranges between the races.

MORTALITY

Our neonatal mortality for 518 consecutive live-born premature infants is 12.7 per cent. Tayler, Phalen, and Dyer of Denver reported a 16 per cent mortality for 480 consecutive live-born infants.[3] New York City hospitals reported a mortality of 17.1 per cent in 1945.[1] Our mortality in the different weight groups is as follows: under 1,000 grams, 87.5 per cent; 1,000 to 1,500 grams, 35.5 per cent; 1,500 to 2,000 grams, 13.5 per cent; and 2,000 to 2,500 grams, 0.3 per cent. This is demonstrated on Chart III. In Bain and Hubbard's report on hospitals, the mortality was 89.6 per cent, 54.4 per cent, 22.8 per cent, and 7.3 per cent, respectively.[4] The Denver group reports 228 cases with a mortality of 91 per cent, 38 per cent, 15 per cent, and 3 per cent, respectively.[3]

It is interesting to review the premature mortality of a few years ago. In 1937, there were 157 premature births in Charity Hospital with a mortality of 85.3 per cent. In 1938, the mortality dropped to 73.6 per cent. This was sur-

CHART III. COMBINED MORTALITY IN THE DIFFERENT WEIGHT GROUPS

WEIGHT (GM.)	<1,000	DEATHS	1,000-1,500	DEATHS	1,500-2,000	DEATHS	2,000-2,500	DEATHS	TOTAL	DEATHS
Month										
1	3	3	4	1	10	2	27	1	44	7
2	4	3	6	2	13	1	26	0	49	6
3	3	3	6	3	11	1	20	0	40	7
4	4	4	4	2	6	2	30	0	44	8
5	4	4	2	0	8	0	32	0	46	4
6	3	3	4	0	9	1	32	0	48	4
7	6	5	3	1	11	1	27	0	47	7
8	4	3	2	0	9	2	27	0	41	5
9	1	1	3	3	6	1	21	0	31	5
10	3	3	2	1	6	0	42	0	53	4
11	3	2	4	1	8	1	25	0	40	4
12	2	1	5	2	7	2	21	0	35	5
Total	40	35	45	16	104	14	330	1	518	66
Mortality		87.5%		35.5%		13.5%		0.3%		12.7%

mised to be due to the segregation of premature from full-term babies for the first time. In 1939, graduate nurses were assigned to premature care and the mortality dropped to 59.3 per cent. In 1940, the mortality was 42.2 per cent which was attributed to the new headquarters and improved conditions for isolation.[5]

Of our 518 premature babies, 7.7 per cent weighed less than 1,000 grams, 8.6 per cent weighed from 1,000 to 1,500 grams, 20.1 per cent weighed from 1,500 to 2,000 grams, and 63.7 per cent weighed from 2,000 to 2,500 grams. These percentages are very similar to those reported by the Children's Bureau in 1948. They reported 6.8 per cent, 9.9 per cent, 20.2 per cent, and 63.1 per cent, respectively. The total fatality for premature babies in 323 hospitals was 21.5 per cent.[4]

CAUSES OF DEATH

In our series there were sixty-six deaths. Prematurity was considered as the cause of death in thirty-eight cases. This is admittedly a poor term but on post-mortem examination no other demonstrable cause of death was found. Fifteen died of congenital atelectasis. Five deaths were due to intracranial hemorrhage, three to sclerema, and five to congenital abnormalities. These abnormalities were atresia of the esophagus, congenital heart disease, atresia of the bile ducts, polycystic kidneys, and anencephalus. Bronchopneumonia was a contributary cause of death in two of these cases. Forty-five deaths (68.1 per cent) were within the first twenty-four hours. Autopsies were obtained in 67 per cent of the deaths.

In 1942 in the Charity Hospital group, prematurity alone accounted for 28 per cent of the deaths. Bronchopneumonia was the cause in 15 per cent. Other acute respiratory diseases and otitis media accounted for 18.6 per cent. Diarrhea was responsible for 12.4 per cent of the mortality. Cerebral injury accounted for 11 per cent and syphilis for 4.6 per cent of the deaths.[5]

According to Tyson, babies who are born dead or who die within the first two days of life, in most instances die as a result of complications of pregnancy, labor, and delivery. The responsibility for such deaths cannot always be attributed to one definite factor but is usually a combination of one or more. In

his experience he found that heroic efforts under these conditions will save only a few babies.[6]

Since 1942, chemotherapy has played a tremendous role in eliminating the mortality due to pneumonia and other respiratory infections. The incidence of infection is lower and when it does occur, fatality is rare.

PREMATURE ROUTINE

All the premature infants considered in this paper were born at Kings County Hospital. Babies weighing less than 1,814 grams at birth and those in poor condition are placed in incubators immediately. Oxygen is administered to all initially and for as long a period as necessary. Some very small infants are given continuous oxygen for as long as one month. Vitamin K is given intramuscularly upon admission to the nursery in doses of 2.5 mg. immediately and every twelve hours for three days. Mothers receive vitamin K routinely before delivery. Initial resuscitation is performed by the obstetrician. Nasopharyngeal suction is performed as necessary thereafter by the graduate nurse especially trained in premature care. Only rarely is laryngoscopic examination and tracheal suction performed. It is felt that unless there is a definite tracheal plug the procedure does little to alleviate atelectasis in very small infants. The trauma that the procedure entails even in expert hands on tiny infants and the excessive handling is felt to be more detrimental than beneficial, in our brief survey.

Nothing is given by mouth for twenty-four hours to babies weighing less than 1,361 grams, and for twelve hours to heavier babies. Then fluids are started in this manner:

Glucose water	1 dr. at the 24 hour
Distilled water	1 dr. at the 25 hour
Glucose water	2 dr. at the 26 hour
Distilled water	2 dr. at the 27 hour
Glucose water	4 dr. at the 28 hour
Distilled water	4 dr. at the 29 hour

The formula is started at 25 per cent Standard Formula 75 per cent distilled water 5 dr. ×3×8 for smallest babies. The larger ones start on 50 per cent Standard Formula 50 per cent distilled water 6 dr. ×3×3. This is followed by 100 per cent Standard Formula 1 oz. ×3×8; 5 per cent glucose in Ringer's lactate may be used instead of distilled water to help prevent the metabolic acidosis commonly found in premature infants. A one part evaporated milk to two parts boiled water formula with two tablespoonfuls of Dextri-Maltose is used to start. The concentration is gradually increased as the child demands it. Gavage feedings are given only to very small, weak infants and to larger babies only when necessary, as during infections. The formula averages 120 or more calories per kilogram initially. Vitamins are started at two weeks of age. A water-miscible multivitamin preparation has been used satisfactorily.

Blood transfusions are given to almost all premature infants under 1,361 grams to alleviate anemia of prematurity. These transfusions of 20 c.c. per kilogram are usually given when the babies are one month old and shortly before discharge from the nursery.

No drugs are used unless absolutely necessary. Caffeine sodium benzoate is the stimulant most frequently used and it is administered in a minims 2 dosage. It is given only when the child shows signs of respiratory irregularity or failure. When penicillin is indicated, it is given orally, usually mixed with the formula in 50,000 unit doses every three or four hours. Aureomycin has been used successfully for otitis media and pustular rashes. It is administered in doses of 80 mg. per kilogram diluted with distilled water and given with 1 dram of Creamalin. No severe gastric irritation or diarrhea has been encountered as yet.

The baby's future home is investigated by the social service to assist the parents in providing an environment which is suitable for a very small infant. The visiting nurse calls on the mother and baby shortly after they arrive home. The babies are discharged to our pediatric clinic for monthly follow-up examinations. The mothers also may bring their babies to the well-baby clinic provided by the Board of Health. This system of follow-up is being encouraged, but many mothers wait until the child is really ill before seeking aid. Education and encouragement may help to solve this problem.

SUMMARY

A survey of 518 consecutive premature infants has been made at Kings County Hospital. Since there are a great number of Negro patients in this hospital, it is possible to make a fair comparison of Negro and white premature infants with special reference to incidence, size, and mortality.

It was found that the incidence of prematurity among 3,872 patients was 20 per cent for the Negro race and 15.5 per cent for the white race. However, it is proposed that the weight standards for Negro premature infants be lowered to 2,350 grams. Under this standard the incidence of prematurity for the Negro race falls to 15.2 per cent in our series.

The total premature mortality for the year 1949 (518 babies) is 12.7 per cent. This compares quite favorably with other reports in recent publications. The mortality is shown in the different weight groups with a newly proposed grouping for premature Negro infants.

The causes of death are listed and compared with the causes of death at Charity Hospital in 1942. The effect of chemotherapy is evidenced by the lowered mortality due to infection.

A brief outline of the premature routine at Kings County Hospital is given.

REFERENCES

1. Dunham, Ethel C.: Premature Infants, Federal Security Agency, Children's Bureau Publication 325, 1948, p. 2.
2. Brown, Estelle W., Lyon, R. A., and Anderson, Nina A. Causes of Prematurity: IV. Influence of Maternal Illness on the Incidence of Prematurity, Employment of a New Criterion of Prematurity for the Negro Race, Am. J. Dis. Child. 70: 314, 1945.
3. Tayler, Stewart E., Phalen, James R., and Dyer, Harold: Effect of Obstetric Difficulties and Maternal Diseases on the Premature Infant Mortality. J. A. M. A. 141: 904, 1949.
4. Bain, Katherine, Hubbard, J. P., and Pennell, Maryland: Hospital Fatality Rates for Premature Infants, Pediatrics 4: 454, 1949.
5. Flax, Lee, Levert, Edward L., and Strong, Robert A.: A Study of Premature Mortality, J. PEDIAT. 21: 717, 1942.
6. Tyson, R. M.: A Fifteen-Year Study of Prematurity, J. PEDIAT. 28: 648, 1946.

DEHYDRATED BANANA IN THE DIETETIC MANAGEMENT OF DIARRHEAS OF INFANCY

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THE efficacy of fruit in the treatment of diarrhea has been a matter of common knowledge in Europe for many years.[1] The apple, the most popular of the fruits, was prescribed subsequently in European hospitals with favorable results.[2-4] More recently, the banana has superseded the apple in popularity and several clinical investigations in Europe on its use have been published.[5-7] In the past decade, several American workers have reported on the successful use of ripe banana and of dehydrated banana powder in the treatment of celiac disease,[8] sprue,[9, 10] and other acute digestive disorders,[11] including diarrhea of specific and nonspecific origin.[12-15]

The purpose of this study, conducted during the summer months of 1949, was to determine whether the favorable results in the management of nonspecific diarrhea reported by Joslin,[12, 13] Brubaker,[16] and several other investigators[17, 18] could be confirmed by us with an improved form of dehydrated banana.* It would seem from the results of this study that in the patients observed, dehydrated banana was an important factor in the rapid amelioration of symptoms. Our results corroborate the findings of these other investigators.

EXPERIMENTAL DATA

Subjects.—Forty children, ranging in age from one month to one year, were observed on the wards of the Kings County Hospital in Brooklyn, New York, during the summer of 1949. They were admitted for a primary diarrhea of nonspecific origin, for which there was no indication for sulfonamides or antibiotics. The predominant presenting symptoms were frequent loose stools, fever, abdominal distress, convulsions, and toxicosis.

Alternate patients admitted to the hospital with these findings were placed on a trial regime incorporating dehydrated banana flakes. The other twenty children were treated according to usual hospital practice, and served as a control group.

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*The dehydrated banana used in these studies is a canned product known as Kanana Banana Flakes, manufactured by Kannengiesser & Company. It is pure ripe banana, dehydrated, reportedly with little loss of the nutritional characteristics of the original fruit.

According to information provided by the manufacturer, it is prepared as follows: The washed and peeled banana is reduced to a pulp and fed onto a revolving drum which is heated to approximately 103° C. Dehydration occurs in about 20 seconds. In some instances the process is shortened to 3 seconds at approximately 120° C. The resultant thin sheet is broken into flakes. The degree of heat used is just below that which would damage significantly the vitamins or esters, caramelize the sugar, or affect the color.

TABLE I. SUMMARY OF DATA ON TWENTY INFANTS TREATED WITH DEHYDRATED BANANA

CASE NO.	AGE (MO.)	DIARRHEAL DAYS PRIOR TO THERAPY	AVERAGE NO. STOOLS/DAY PRIOR TO THERAPY	WEIGHT ON ADMISSION		TEMPERATURE ON ADMISSION (° F.)	AFTER 24 HOURS					AFTER 48 HOURS					AFTER 72 HOURS					RESULTS†		
							STOOLS*			WEIGHT		STOOLS*			WEIGHT		STOOLS*			WEIGHT				
				LB.	OZ.		NO./DAY	MUCOUS	CONSISTENCY	LB.	OZ.	NO./DAY	MUCOUS	CONSISTENCY	LB.	OZ.	NO./DAY	MUCOUS	CONSISTENCY	LB.	OZ.	RATING	WEIGHT (OZ.)	DURATION OF DIARRHEA (DA.)
1	2	5	12	8	13	102	4	++	L	9	7	7	+	S	9	10	3	0	F	9	12	G	+15	3
2	2	10	3	9	12	98.6	1	0	L	9	12	1	0	F	9	12	2	0	F	9	13	G	+ 1	2
3	6	4	5	16	3	100	2	0	L	16	3	1	0	L	16	5	1	0	F	16	4	G	+ 1	3
4	2	4	4	14	7	102	2	0	L	14	7	2	0	F	14	8	2	0	F	14	8½	G	+ 1½	2
5	9	3	12	17	7	101	6	0	W	17	10	2	0	L	18	0	0	0	0	18	2	G	+11	3
6	1	2	6	7	2	102	5	0	W	7	2	1	0	S	7	2	5	0	F	7	4	G	+ 2	3
7	1	3	6	8	0	100	2	0	L	8	0	11	0	L	8	2	1	0	L	8	3	F	+ 3	4
8	5	4	10	14	0	103	2	+	L	13	14	3	0	L	13	12	5	0	S	14	3	G	+ 3	4
9	5	2	5	12	3	104	2	0	L	12	3	3	0	L	12	5	1	0	F	12	7	G	+ 4	3
10	1	3	7	6	0	98.6	5	0	L	6	2	4	0	L	6	2	4	0	F	6	2	G	+ 2	3
11	4	1	6	13	5	98.6	4	++	L	13	5	4	+	L	12	15	5	0	S	12	13	F	− 8	4
12	2	2	6	6	12	98.6	2	0	S	6	11	2	0	L	6	11	2	0	F	6	11	G	− 1	3
13	5	4	11	8	8	102	2	0	L	8	12	1	0	S	8	12	1	0	S	8	14	G	+ 6	2
14	2	3	3	9	3	98.6	1	0	F	9	1	4	0	L	9	0	4	0	S	9	0	F	− 3	4
15	6	2	7	17	0	101	3	++	L	17	0	3	0	S	16	12	1	0	F	17	10	G	+10	3
16	3	10	6	12	2	103	1	++	S	12	2	4	0	L	13	0	2	0	F	13	5	G	+19	3
17	12	2	7	23	0	102.4	3	+	L	22	14	3	0	S	22	14	0	0	0	23	0	G	0	2
18	10	1	3	22	2	99	2	0	L	22	0	0	0	0	22	4	1	0	F	22	6	G	+ 2	1
19	9	3	7	27	14	104	1	+	L	27	8	4	+	W	27	2	1	0	F	27	6	G	− 8	3
20	1	2	2	8	7	99	3	++	L	8	7	2	+	L	8	7	1	0	F	8	9	G	+ 2	3

*_Mucous:_ 0 = None; + = Minimal Amount; ++ = Moderate Amount; +++ = Marked Amount. _Consistency:_ F = Formed; S = Semisolid; L = Loose; W = Watery.

†_Rating:_ G = Good; F = Fair; P = Poor. _Duration of Diarrhea:_ Calculated from institution of treatment.

TABLE II. CONTROL GROUP: SUMMARY OF DATA ON TWENTY INFANTS TREATED ACCORDING TO ESTABLISHED PROCEDURES (NO DEHYDRATED BANANA GIVEN)

CASE NO.	AGE	DIARRHEAL DAYS PRIOR TO THERAPY	AVERAGE NO. OF STOOLS/DAY PRIOR TO THERAPY	WEIGHT ON ADMISSION		TEMPERATURE ON ADMISSION (°F.)	AFTER 24 HOURS					AFTER 48 HOURS					AFTER 72 HOURS					RESULTS†		
							STOOLS*			WEIGHT		STOOLS*			WEIGHT		STOOLS*			WEIGHT				
				LB.	OZ.		NO./DAY	MUCOUS	CONSISTENCY	LB.	OZ.	NO./DAY	MUCOUS	CONSISTENCY	LB.	OZ.	NO./DAY	MUCOUS	CONSISTENCY	LB.	OZ.	RATING	GAIN OR LOSS IN WEIGHT (OZ.)	DURATION OF DIARRHEA (DA.)
1	6 da.	1	6	4	6	102	8	0	S	4	10	3	0	S	4	13	5	0	F	4	13	G	+ 7	3
2	3 mo.	3	3	12	8	100	5	++	L	11	15	2	+	S	11	13	2	0	F	11	13	G	–11	3
3	1 da.	1	6	5	0	99	7	0	L	4	15	8	0	S	4	13	5	0	S	4	14	F	– 2	6
4	5 mo.	1	8	13	6	103	2	0	F	13	6½	2	0	W	13	8	4	0	S	13	8½	F	+ 2.5	6
5	3 wk.	3	8	7	12	100	0	0	0	7	12	3	+	F	7	11	3	0	F	7	10	G	– 2	2
6	3 wk.	3	8	6	2	101	3	++	L	6	10	1	0	L	7	5	2	0	L	7	2	F	+16	4
7	10 mo.	2	6	26	6	103	2	0	S	26	6	4	0	L	26	3	2	0	L	25	10	P	–12	5
8	5 mo.	1	5	14	6	101	1	0	L	14	3	3	0	S	14	0	1	0	S	13	14	F	– 8	7
9	4 mo.	1	10	10	10	101	1	0	F	10	5	6	0	L	10	3	3	0	L	10	3	P	– 7	10
10	4 mo.	2	8	11	6	101.4	2	0	W	11	5	1	0	F	11	6	0	0	0	11	6	G	0	2
11	3 mo.	1	7	8	10	99.6	3	0	F	8	10	1	0	W	9	0	0	0	0	9	2	G	+ 4	3
12	3 mo.	1	12	9	1	101	3	0	F	9	1	2	0	L	9	1	1	0	L	9	3	F	+ 2	5
13	2 mo.	2	2	8	8	99.6	2	+	W	8	8	3	+	L	8	8	2	0	S	8	8	F	0	4
14	1 mo.	7	8	7	4	99	2	0	L	7	5	2	0	L	7	3	1	0	W	7	6	P	+ 2	4
15	6 mo.	1	5	10	7	101.4	0	0	0	10	2	3	0	L	9	15	3	0	L	9	15	P	– 8	12
16	2 wk.	2	8	5	14	102	1	0	L	5	14	Expired											Expired	
17	1 wk.	1	1	5	11	99	3	0	W	5	6	3	0	L	5	1	2	0	W	5	1	P	–10	6
18	12 mo.	3	6	18	14	99	2	0	W	18	8	5	0	L	17	12	2	0	L	17	8	F	–22	5
19	1 mo.	1	10	9	5	100	1	0	L	9	5	2	0	S	9	6	0	0	0	9	4	G	– 1	3
20	4 mo.	7	8	16	12	100	2	0	W	16	12	0	0	0	16	12	0	0	0	17	0	G	+ 4	2

*_Mucous_: 0 = None; + = Minimal Amount; ++ = Moderate Amount; +++ = Marked Amount. _Consistency_: F = Formed; S = Semisolid; L = Loose; W = Watery.

†_Rating_: G = Good; F = Fair; P = Poor. _Duration of Diarrhea_: Calculated from institution of treatment.

Criteria.—The diagnosis of nonspecific diarrhea depended upon negative stool cultures ruling out the common types of specific dysentery. Further verification was sought from specific agglutination tests and blood cultures.

Results were considered good, fair, or poor on the following basis: Those cases were rated "good" which responded to therapy in 72 hours with formed stools, usually no more than three or four a day. Those in whom the intensity of the diarrhea had diminished, but who still had abnormal stools at the end of 72 hours, were rated "fair." Those who did not respond to therapy in 72 hours (i.e., the diarrhea continued in intensity equal to that on admission) were recorded as "poor."

As part of the daily hospital record, the number of stools with their consistency and mucous content, and the weight and temperature of the child were tabulated.

Method.—Trial Group: Almost all the infants were placed immediately on a regimen of 1 level tablespoon (6 Gm., 23 calories) of dehydrated banana flakes per pound (543 Gm.) of body weight per 24 hours. Two ounces (60 c.c.) of water were used to dilute each tablespoon (1:2 dilution). The total amount calculated for the day was divided into nine feedings which were given at 6 A.M., 8 A.M., 10 A.M., 12 noon, 2 P.M., 4 P.M., 6 P.M., 10 P.M., AND 2 A.M. Boiled water was given as often as possible between feedings.

At the end of from 48 to 72 hours, with improvement, the infant was placed on a "transitional" diet consisting of dehydrated banana flakes in a 5 per cent to 7½ per cent skimmed milk formula. For older infants, well-cooked cereal, beef broth, puréed vegetables, and custards were added to the diet at this stage.

In the three cases where the illness was severe, as charactrized by vomiting, marked dehydration, and acidosis, parenteral fluids were given first.

Control Group: The following routine hospital procedure was employed. During a starvation period of from 24 to 48 hours, hydration was maintained by use of clysis or scalp infusion. The latter consisted of (1) 5 per cent glucose in Ringer's lactate solution, (2) 5 per cent Amigen, and (3) 10 per cent dextrose in water solution. After the starvation period, a variety of formulas was given (e.g., protein milk, skimmed milk, or acidified milk); and water or tea was offered between feedings. With further improvement, the infant received a dried or evaporated or whole milk formula, later supplemented by semisolids.

Results.—In the trial group, within 24 hours there was an appreciable reduction in the number of stools, and recovery was sufficient after 48 hours to permit the change to the "transitional" diet.

The average time of complete recovery, calculated from the time of institution of treatment, in the experimental group was 2.9 days as compared with 5.02 days in the control group. (Tables I, II.)

At the end of 72 hours, when an evaluation was made, 17 in the trial series were rated "good," 3 "fair," and 0 "poor;" as against 7 "good," 7 "fair," and 6 "poor" in the control. Included in this last group is one child

who died on the second day of treatment. Sixteen of the children in the trial group demonstrated gains in weight of from 1 to 19 ounces, only 3 showing any loss and one maintaining weight, with an over-all average weight gain of 3.9 ounces. In contrast, the control series showed 9 children with weight losses of from 1 to 22 ounces, one expiring, 3 maintaining their weight, and 7 gaining from 2 to 7 ounces, with an over-all average of 3.38 ounces of weight lost.

DISCUSSION

In this study we attempted to eliminate as many variables as possible. All the children included were under one year of age and were treated in the same hospital, at approximately the same time, where we had constant control of their management and diet. No medications were used. Because nonspecific diarrhea in infants under one year of age is particularly challenging, we limited our study to this age group.

We found it possible to feed concentrated banana during what would usually be the starvation period in the treatment of diarrhea. The carbohydrate (83.48 per cent), protein (6.87 per cent), fat (1.30 per cent), and the appreciable amount of vitamins and minerals* contributed to the child's nutrition. One of the advantages of this type of food is its complete acceptability even to severely ill infants who ordinarily refuse nourishment. This acceptance may be a factor in the persistent weight gains during the acute course of the diarrhea in the infants maintained on dehydrated banana.

No digestive disturbances were observed with any of the children receiving dehydrated banana, although vomiting and gastric distress were observed in the control group with the use of protein, skimmed and dried milks.

Several theories have been advanced as to the reason for the effectiveness of banana in the control of diarrhea. Whether its action is chemical (due to pectin,[19, 20] tannins,[6] and malic[6] or butyric acids[21]), or mechanical[5] (due to the cleansing of the intestines as a result of adsorption of toxic products), or bacteriologic[22, 23] (due to changes effected in the intestinal flora) remains to be determined. Other explanations include as wide a variation as the favoring of the growth of gram-positive organisms[22] or the favoring of the growth of gram-negative organisms,[24] the retention of hydrochloric acid in the stomach due to the action of the banana as a buffer,[25] and the diminution of bacteriolysis in the colon with diminished absorption of bacterial nitrogens.[26] The authors feel that it is probably a combination of several of these factors.

In addition to these known advantages of banana, the dehydrated product, from which the moisture content has been reduced to 5 per cent from 80 per cent, offers two things: its high concentration of nutrition in small bulk, and its hygroscopic character which prevents serious loss of fluids via vomiting and fecal discharge.

SUMMARY AND CONCLUSIONS

1. Twenty infants with diarrheal disease of nonspecific origin were treated with dehydrated banana flakes. A similar group of twenty cases were treated according to well-recognized methods.

*Analysis as accepted by the Council on Foods and Nutrition of the American Medical Association

2. Data are given to show that the trial group treated with the dehydrated banana flakes recovered more rapidly than did the control group. Gains in weight during the acute phase of the illness were noted more frequently.

3. It was observed that dehydrated banana was accepted willingly, served to satisfy hunger, and was well tolerated.

4. The authors conclude that the use of dehydrated banana flakes provides a method of choice in the treatment of nonspecific diarrheas of infancy.

REFERENCES

1. Birnberg, T. L.: Raw Apple Diet in the Treatment of Diarrheal Conditions in Children, Am. J. Dis. Child. **45**: 18, 1933.
2. Moro, E.: Zwei Tage Apfeldiat zur Behandlung diarrhoischer Zustande im Kindesalter, Klin. Wchnschr. **8**: 2414, 1929.
3. Kollman, A.: Apple Diet in Diarrhea of Infants and Children, Med. Welt. **4**: 1067, 1930.
4. Melentieva, E. P.: Raw Apples in the Treatment of Diarrhea in Children, Pediatriya **14**: 424, 1930.
5. Fanconi, G.: Fruit Diet for Acute Digestive Disturbances in Children, Monatschr. f. Kinderh. **49**: 232, 1931.
6. Baumann, T., and Forschner-Boke, H.: Studies on the Therapeutic Action of Apple and Banana Diet, Ztschr. f. Kinderh. **56**: 545, 1934.
7. von Reuss, A.: Raw Fruit Diet in Digestive Disturbances in Childhood, Wien. med. Wchnschr. **88**: 1023, 1938.
8. Haas, S. V.: The Value of the Banana in the Treatment of Celiac Disease, Am. J. Dis. Child. **28**: 421, 1924.
9. Brown, W. C.: Sprue and Its Treatment, London, 1908, John Bale, Sons and Danielsson, Ltd., p. 166.
10. Ashford, B. K.: Relation of the Genus "Monilia" to Certain Fermentative Conditions of the Intestinal Tract in Porto Rico, J. A. M. A. **64**: 1893, 1915.
11. Cornwall, E. E.: The Spastic Colon Diet, Am. J. Digest. Dis. & Nutrition **3**: 773, 1936.
12. Joslin, C. L.: Banana Therapy in Diarrheal Diseases in Infants and Children, South. M. J. **29**: 1007, 1936.
13. Joslin, C. L., Bradley, J. E., and Christensen, T. A.: Banana Therapy in the Diarrheal Diseases of Infants and Children, J. PEDIAT. **12**: 66, 1938.
14. McCormick, R.: Infectious Diarrheas in Children, Memphis M. J. **15**: 54, 1940.
15. Block, L. H., and Tarnowski, A.: Am. J. Digest. Dis. & Nutrition **8**: 3, 1941.
16. Brubaker, E. W.: The Treatment of Acute Diarrheal Disorders of Infancy and Early Childhood With Banana and Banana Powder, J. Michigan M. Soc. **36**: 40, 1937.
17. Wolman, I. J., and Roddy, R. L.: Value of Banana and Banana Powder in the Treatment of Infants and Children Having Diarrhea, Am. J. Dis. Child. **60**: 333, 1940.
18. Bethea, O. W., and Bethea, H.: Banana Diet in the Treatment of Diarrheal Diseases of Adults, Internat. M. Digest. **32**: 369, 1938.
19. Manville, I. A., Bradway, E. M., and McInnis, A. S.: Pectin as a Detoxication Mechanism, Am. J. Digest. Dis. & Nutrition **3**: 570, 1936.
20. Ziegelmayer, W.: Ueber die Adsorptionswirkung der Pektine im Darm, Klin. Wchnschr. **15**: 19, 1936.
21. Bergheim, O., Hanszen, A., and Arnold, L.: The Influence of Fruit Ingestion Before Meals Upon the Bacterial Flora of Stomach and Large Intestine and on Food Allergens, Am. J. Digest. Dis. & Nutrition **3**: 45, 1936.
22. Kahn, B. S.: The Effect of the Banana Powder Feeding on the Fecal Flora of Infants, Arch. Pediat. **50**: 330, 1933.
23. Weinstein, L., and Bogin, M.: The Effect of Banana Feeding on the Intestinal Flora and on Constipation in Children and Adults, Rev. Gastroenterol. **6**: 21, 1939.
24. Arnold, L.: The Influence of Cornstarch, Sucrose, and Banana Powder on the Acid Base Equilibrium and Bacterial Flora of the Gastrointestinal Tract of the Rat, J. Infect. Dis. **51**: 556, 1932.
25. Hanszen, A.: The Bactericidal Powder of the Stomach and Some Factors Which Influence It, Am. J. Digest. Dis. & Nutrition **1**: 725, 1934.
26. Higgins, H. L.: The Feeding of Bananas and of Squash to Infants and Children, Am. J. Dis. Child. **46**: 446, 1933.

PURPURA FOLLOWING EXPOSURE TO DDT

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THE general consensus has been that, used with reasonable care, preparations containing DDT—2, 2 bis (*p*-chlorophenyl)—1, 1, 1—trichloroethane, do not present significant toxic hazards to human beings. The purpose of this paper is to report the occurrence of purpura in five children following exposure to DDT products.

CASE REPORTS

CASE 1.*—C. W., a 2½-year-old white female child, was admitted to Babies and Childrens Hospital of Cleveland Sept. 16, 1946, with the complaint of "pinpoint hemorrhages" in the skin of two days' duration. She was perfectly well until Sept. 14, 1946, when she developed numerous petechiae over the face, arms, knees, legs, and buttocks. Several petechiae were also noted on the gums and tongue. The following day, Sept. 15, 1946, there was a progression in the number and spread of the petechiae as well as the appearance of several small ecchymoses on the forehead.

The patient was active, alert, played well, and possessed a good appetite. There was no evidence of upper-respiratory infection and she did not appear ill. There was nothing indicative of an allergic background in the family history. She had received no drugs in the preceding six months.

However, the child was known to have been exposed to DDT several days before the onset of symptoms. Her grandparent's home was thoroughly sprayed with DDT spray solutions and DDT aerosol bombs on Sept. 4, 1946, and was completely closed and uninhabited for the next six days. The home was reoccupied on Sept. 10, 1946, and the patient lived and played about this DDT-sprayed home for the ensuing three days. The symptoms of purpura developed the very next day, Sept. 14, 1946.

On admission she was found to be well developed and nourished and did not appear acutely or chronically ill. The temperature was 37.1° C. Physical examination was negative except for the presence of petechiae over the face, buttocks, and all the extremities. Several minute petechiae were present over the buccal mucosa and hard palate. There were numerous small ecchymoses over the arms and legs.

Laboratory studies were as follows: erythrocytes 3,430,000 per cubic millimeter, hemoglobin 10.0 Gm. per 100 ml., leucocytes 12,200 per cubic millimeter, with a differential count of: segmented neutrophiles 46 per cent, lymphocytes 48 per cent, monocytes 5 per cent, and eosinophiles 1 per cent. The bleeding time was 20 minutes and the clot retraction prolonged. Platelet count was zero. The tourniquet test was positive.

No specific therapy was instituted and by the fourth hospital day there was definite clearing of the skin. The platelet count at this time was 17,250 per cubic millimeter, and 114,300 per cubic millimeter by the fifth day. Complete disappearance of the petechiae and ecchymoses occurred in the next five days. The patient was discharged on the eleventh hospital day. Laboratory

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*Cases 1 and 3 are presented through the courtesy of Dr. J. I. Hartman. Case 5 is presented through the courtesy of Dr. R. W. Heinle, Cleveland.

studies at this time were: erythrocytes 3,480,000 per cubic millimeter, hemoglobin 10.0 Gm. per 100 ml., and platelets 420,000 per cubic millimeter. The bleeding time was 4 minutes, clotting time 5 minutes, and clot retraction normal.

CASE 2.—J. K., a 22-month-old white female child, was admitted to Babies and Childrens Hospital of Cleveland on April 22, 1948, with a chief complaint of a rash over the extremities of one week's duration. Two weeks prior to admission the patient became irritable, nervous, and anorexic. Her mother thought she felt feverish, although there were no signs of an upper-respiratory infection. The day following the onset of symptoms the child had a generalized tonic-clonic convulsion lasting 15 minutes. There were no further convulsive episodes in the next five days and the child did not appear to have a fever. However, anorexia, irritability, and nervousness persisted. One week before admission she developed a purpuric eruption over all the extremities with a few scattered lesions over the abdomen. Some of these faded to a brownish hue in the ensuing days but new lesions were noted to erupt on the extremities.

The child had not been ill prior to this illness and had not received any medication. However, the mother disclosed that the child's bed and mattress were thoroughly sprayed with an aerosol bomb containing DDT, Pyrethrum extract, and difluorodichloro methane (Freon) in December, 1947, January, 1948, and one month prior to onset of symptoms. The odor of the aerosol bomb was always quite pronounced about the bed. With the onset of the rash the child was removed to another bedroom as the mother suspected an allergy to the DDT bomb. A similar purpuric eruption was noted approximately two weeks after the initial use of the DDT bomb, but the child's mother thought these were insect bites at the time.

There was no family history of allegry or blood dyscrasias. On admission she was found to be well developed and nourished, irritable but not particularly ill. The temperature was 37.2° C. Examination was negative except for the presence of numerous 2 × 2 cm. ecchymoses over all the extremities. Some of these appeared to be old and faded, but the majority were relatively new lesions. The submandibular and angular lymph nodes were moderately enlarged and slightly tender. There was no evidence of upper-respiratory infection, however.

Laboratory studies showed: erythrocytes 2,600,000 per cubic millimeter, hemoglobin 11.0 Gm. per 100 ml., leucocytes 19,000 per cubic millimeter with a differential count of: segmented neutrophiles 29 per cent, unsegmented neutrophiles 2 per cent, and lymphocytes 69 per cent. The bleeding time, clotting time, and clot retraction were all normal. The Rumpel Leede test was positive. Platelets were adequate. Urinalysis was negative. Roentgenograms of the chest and skeleton were interpreted as normal.

The patient received no therapy and by the fifth hospital day was practically free of purpuric lesions. At this time the erythrocyte count was 2,700,000 per cubic millimeter, hemoglobin 11.0 Gm. per 100 ml., and leucocytes 10,200 per cubic millimeter. The differential count now was: segmented neutrophiles 50 per cent, unsegmented neutrophiles 3 per cent, lymphocytes 45 per cent, monocytes 1 per cent, and eosinophiles 1 per cent. She was discharged on the sixth hospital day.

CASE 3.—L. H., a 2½-year-old white female child, was admitted to Babies and Childrens Hospital of Cleveland, Dec. 6, 1949, with the complaint of petechial hemorrhages and easy bruising. These signs were first noticed in September, 1948, at which time she appeared to be riddled with "black and blue" marks and petechiae. However, she did not appear ill and the lesions cleared considerably over a period of two weeks. In September, 1949, two months prior to admission, she had a fall and sustained an enormous bruise over the left

inguinal region. This bruising tendency continued for the next two months and was associated with the appearance of numerous petechial hemorrhages over the body. One week before entry to the hospital she developed extreme irritability, anorexia, and slept poorly. There was no fever nor signs of upper-respiratory infection associated with these symptoms.

The patient had not been ill and had received no drugs. However, the father revealed that the child had repeated exposures to DDT solutions for more than a year. He had thoroughly and intensively sprayed the basement with a 5 per cent DDT solution in August, 1948. The patient utilized the basement as a playroom and spent a considerable portion of each day there. She was said to chew on nails that were sprayed with the DDT solution. Again in September, 1949, a 5 per cent DDT spray was used, this time spraying the basement and kitchen closet. The closet was a storage place for the child's toys and she was in and out of the closet repeatedly. The odor of the DDT solution was still quite prominent about the closet. In retrospect, the parents recollect that the patient lost the tendency to bruise whenever she spent short vacation periods at her grandmother's home in a neighboring community.

On admission she was quite irritable and the temperature was 38.0° C. Physical examination revealed moderate nontender enlargement of the posterior cervical lymph nodes. Small pinpoint petechiae were scattered throughout the mucous membranes of the conjunctivae, nose, mouth, and pharynx. Petechiae were also widely distributed over the face, neck, chest, and all extremities. Several small ecchymoses were present over the extremities with one large ecchymotic area over the left flank. There was no significant lymphadenopathy nor hepatosplenomegaly.

Laboratory studies were as follows: erythrocytes 4,440,000 per cubic millimeter, hemoglobin 11.0 Gm. per 100 ml., leucocytes 12,800 per cubic millimeter. with a differential count of: segmented neutrophiles 16 per cent, unsegmented neutrophiles 5 per cent, lymphocytes 74 per cent, and blast cells 5 per cent. The bleeding time was 16 minutes, clotting time 10 minutes, and moderate clot retraction in five hours. Platelets were 13,000 per cubic millimeter. The Rumpel Leede test was strongly positive. The prothrombin time was 98 per cent of normal. Heterophil antibody titer was 1:32 and 1:16. Examination of the sternal marrow was interpreted as normal. Megakaryocytes were abundant and morphologically normal in appearance. Roentgenograms of the long bones were negative.

The child received no therapy and her hospital course was uneventful. By the third day the temperature was normal and the petechiae and ecchymoses were clearing. Bleeding time and clot retraction were normal by the fourth day and the petechiae and ecchymoses disappeared by the tenth hospital day. A platelet count at this time was 34,000 per cubic millimeter. She was discharged on the eleventh hospital day.

Since discharge she has lived with her grandmother and remained free of purpuric lesions. A recent platelet count revealed 66,000 per cubic millimeter.

CASE 4.—S. K., a 17-month-old white male child, was admitted to Babies and Childrens Hospital of Cleveland on Jan. 24, 1950. He was well until the latter part of December, 1949, when he developed an unsteady gait and frequently stumbled and fell. Prior to this time he walked well and first walked alone at one year of age. On Jan. 20, 1950, he developed petechiae and ecchymoses over the face, chest, and extremities. There was no associated fever or upper-respiratory infection. The next day the petechiae and ecchymoses became more intense and more widespread. He was hospitalized at another hospital where a tentative diagnosis of leucemia was made. The patient was transferred to this hospital on Jan. 24, 1950.

There was no history of recent illnesses or drug therapy. No allergic background was obtained in the family history. Specific questioning revealed that the child frequently played with and chewed on his food jars which had been intensively sprayed with a 5 per cent DDT solution. His mother was not aware that these jars had been sprayed with the DDT solution and permitted the child to chew on them at will.

On admission he was well developed and well nourished and appeared acutely ill. The temperature was 37.0° C. Physical examination revealed multiple petechial hemorrhagic spots over the entire body. Large ecchymoses were present on the forehead, chest, and extremities, with a large shieldlike ecchymotic lesion over the sternum. The latter appeared to be due to a sternal aspiration performed at the other hospital. The spleen was palpable at the costal cage. The remainder of the examination was not remarkable.

Laboratory studies were as follows: erythrocytes 4,430,000 per cubic millimeter, hemoglobin 11.2 Gm. per 100 ml., leucocytes 13,600 per cubic millimeter, with a differential count of: segmented neutrophiles 36 per cent, and lymphocytes 64 per cent. The bleeding time was 20 minutes, clotting time 3 minutes, and no clot retraction in 24 hours. No platelets were seen by the direct smear method. Sternal marrow examination revealed an increase up to 50 per cent of small, mature lymphocytes and the presence of numerous megakaryocytes.

Therapy consisted of ascorbic acid 100 mg. and rutin 40 mg. daily for a period of ten days. By the ninth hospital day the patient was free of petechiae and ecchymoses except for a shieldlike, bluish discoloration over the sternal puncture site. The leucocyte count was 10,000 per cubic millimeter, with 42 per cent segmented neutrophiles and 58 per cent lymphocytes. Bleeding time was 2 minutes, clotting time 3 minutes, and clot retraction normal. There were 200,000 platelets per cubic millimeter. He was discharged on the 11th hospital day.

CASE 5.—C. R., a 3-year-old white male child, was admitted to another hospital on Jan. 28, 1950, with the complaint of epistaxis and easy bruising. He was well until one week prior to admission when he developed petechiae over the extremities, epistaxis, and several ecchymoses over the back and legs. There was no associated fever or signs of upper-respiratory infection. His stools were noticeably black on several occasions.

There was no history of recent illness or drug therapy. One month before the onset of symptoms he had developed an unexplained transient urticarial eruption. No allergic background was obtained in the family history. Further questioning, however, revealed that the child had an extensive exposure to a 5 per cent DDT solution. The household furniture, rugs, floors, and clothes closets were thoroughly sprayed with DDT in the summer of 1949, and again approximately two months before the development of symptoms.

On admission he appeared well nourished, irritable, and the temperature was 37.5° C. Physical examination revealed numerous petechiae over the palate and posterior pharyngeal wall. Petechiae and ecchymoses were present over all extremities. There was no hepatosplenomegaly or significant lymphadenopathy.

Laboratory studies were as follows: erythrocytes 4,710,000 per cubic millimeter, hemoglobin 13.0 Gm. per 100 ml., leucocytes 8,300 per cubic millimeter, with a differential count of: segmented neutrophiles 39 per cent, unsegmented neutrophiles 5 per cent, lymphocytes 48 per cent, monocytes 6 per cent, and eosinophiles 2 per cent. The bleeding time was 40 minutes and the clotting time 5 minutes. Clot retraction was complete in 24 hours. Platelets were 50,000 per cubic millimeter. Examination of the bone marrow was interpreted as normal. Megakaryocytes were present in at least normal or, perhaps, increased numbers.

His hospital course was not particularly eventful. There was gradual disappearance of the petechiae and ecchymoses, but there was no significant rise in the number of platelets. Several small blood transfusions were given and the patient was discharged on the seventeenth hospital day. The platelet count was 30,000 per cubic millimeter at the time of discharge.

He was seen again March 1, 1950, and was free of petechiae and ecchymoses. The erythrocytes numbered 4,590,000 per cubic millimeter, hemoglobin 12.5 Gm. per 100 ml., and the leucocytes 8,350 per cubic millimeter. The platelet count was 110,160 per cubic millimeter. Bleeding time was 3 minutes and the clotting time 6 minutes. Clot retraction started within one hour but was slight within 7 hours.

DISCUSSION

Since DDT was first introduced in England in 1939 and in this country in 1942, numerous investigators[1-6] have studied the toxic effects of the product on different species of warm-blooded animals. The symptomatology of animals suffering from DDT poisoning is characterized by anorexia, generalized tremors, nervousness, hyperexcitability, impaired coordination, clonic-tonic type of convulsions, and coma ending in death. The convulsions are said to resemble closely those seen in strychnine poisoning in that they can be elicited by mechanical stimuli, such as sudden noise and jarring.

According to Neal,[7] studies on animals suffering from DDT toxicity failed to reveal definite evidence of an injurious effect on the blood picture, blood chemistry, or blood-forming organs. Studies of the blood constituents during chronic subacute DDT poisoning in dogs revealed no characteristic effect on the blood picture other than a drop in hemoglobin over a period of days resulting in an hypochronic anemia. It is thought probable that this anemia is the direct result of dietary deficiencies resulting from prolonged anorexia, tremors, and convulsions. However, in rats there was an occasional fall in hemoglobin and leucopenia, the per cent of lymphocytes falling but the per cent of neutrophiles rising. In rabbits, the leucocyte count rose, with a sharp increase in the percentage of neutrophiles. Atypical lymphoid cells, a high normoblast count, or eosinophilia have been observed in a few animals.

With regard to the toxicity of DDT for human beings, most investigators feel that it is of a sufficiently low order to permit the use of DDT without danger if reasonable precautions are taken. It has been generally accepted, however, that DDT can be absorbed through the gastrointestinal tract, the respiratory tract, and also through the skin, if applied in oily solutions. This is in contrast to the dry-powder which is not absorbed through the skin. It is Neal's[7] opinion also that following repeated exposure of human beings to small amounts of DDT there is an accumulation of the chemical in the tissues but practically no cumulative or cell damage.

Nevertheless, isolated reports of DDT toxicity in man have appeared in the literature.[8-11] Case[12] probably presented the first positive evidence, suggesting that DDT products are potential toxins to the bone marrow as well as to other organs. He reported the toxic effects of a 2 per cent solution of DDT on two male subjects exposed for ninety-six hours in a specially constructed steel

chamber and under special conditions; these consisted of an oily surface, large areas of skin exposed, and high temperature and relative humidity. The hematologic effect noted included an increased destruction of erythrocytes, a diminution in the mean corpuscular hemoglobin, reticulocytosis, transitory polymorphonuclear leucopenia accompanied by a lymphocytosis, and the appearance of immature white cells. The hematologic values returned to original limits in approximately twenty-six days following exposure.

Wright and associates[13] submit further proof that DDT products may affect the bone marrow. These authors present the case of a 22-year-old student who developed fever, ulceration of the tongue, submandibular and angular lymphadenopathy, and agranulocytosis following exposure to the spray of a DDT Pyrethrum aerosol bomb.

Thus, with the gradually accumulating evidence that DDT mixtures are capable of affecting the bone marrow and blood picture in animals and in human beings, it appears reasonable that DDT probably should be included in that group of drugs known to produce purpura. Even though Neal and Von Oettingen[7] state that DDT is not known to exert a sensitizing effect on the skin or produce other allergic reactions, it seems more than mere coincidence that five children should develop the clinical picture of purpura following exposure to this drug. The fact that three of the patients exhibited signs of irritability, nervousness, impaired coordination, or clonic-tonic convulsions perhaps strengthens the relation of the DDT to the purpura.

Means were not available to measure the amount of metabolite, DDA present in the urine and thus lend support to DDT as the noxious agent. It has been shown, however, that in both animals[14] and in human beings,[15] part of the ingested DDT is metabolized to DDA—di (*p*-chlorophenyl) acetic acid, and excreted in the urine. Maximum excretion of this metabolite occurs in 48 hours; it decreases rapidly on the third and fourth days, and diminishes gradually during the subsequent ten days.

Any of the ingredients used in the preparation of the DDT mixture might be incriminated as the offending agent. However, there has been no evidence to suggest any injurious effect of Pyrethrum on the blood elements, and neither animals nor human beings are said to suffer apparent deleterious effects following exposure to high concentrations of Freon.[13] Two of the patients in this group were exposed to mixtures containing DDT, Thanite, and deodorized kerosene. However, no adverse effects have been shown in laboratory animals and human subjects following acute and subacute exposures to 5 per cent Thanite (82 per cent isobornyl thiocyanoacetate and 18 per cent other active terpenes).[16]

Thus, while it is impossible to state with certainty that DDT alone was responsible for the production of the purpura, the evidence on hand would appear to support this possibility. All five children had a significant history of definite and extensive exposure to DDT spray products and in four of five cases the purpuric manifestations were extensive and associated with marked thrombocytopenia. Furthermore, there was nothing to indicate infection or other drugs as possible etiological agents capable of producing purpura. While the various

vehicles used in the preparation of the DDT spray products cannot be excluded as offending agents, the following assumption is probably justified. Due to the variability of the composition of the DDT products and the generally accepted innocuousness of the vehicles employed in their preparation, the presumption must be that exposure to DDT was responsible for the development of purpuric manifestations.

SUMMARY

Five cases of purpura occurring in children following exposure to DDT mixtures are presented.

The known toxic effects of DDT in animals and human beings are briefly discussed.

The purpuric manifestations were extensive and associated with marked thrombocytopenia in four of five cases.

Recovery is relatively prompt with a change of environment and without specific medication.

The only noxious agent that might be incriminated was a DDT spray product.

As all available data indicate the innocuousness of the vehicles employed, the DDT appears to be responsible for the development of purpura.

REFERENCES

1. Draize, J. H., Woodard, G. W., Fitzhugh, O. G., Nelson, A. A., Smith, R. B., Jr., and Calvery, H. O.: Summary of Toxicological Studies of the Insecticide DDT, Chem. and Eng. News **22**: 1503, 1944.
2. Woodard, G., Nelson, A. A., and Calvery, H. O.: Acute and Subacute Toxicity of DDT (2,2,-bis [*p*-chlorophenyl]-1,1,1-Trichloroethane) to Laboratory Animals, J. Pharmacol. & Exper. Therap. **82**: 152, 1944.
3. Draize, J. H., Nelson, A. A., and Calvery, H. O.: The Percutaneous Absorption of DDT (2,2-bis [*p*-chlorophenyl]-1,1,1-Trichloroethane) in Laboratory Animals, J. Pharmacol. & Exper. Therap. **82**: 159, 1944.
4. Neal, P. A.: A Report on the Toxicity to Warm-blooded Animals of Aerosols, Mists, and Dusting Powders Containing DDT, Soap and Sanitary Chemicals **21**: 99, 1945.
5. Cameron, G. R., and Burgess, F.: The Toxicity of (2,2-bis [*p*-chlorophenyl] 1,1,1-Trichloroethane) DDT, Brit. M. J. **1**: 865, 1945.
6. Neal, P. A., von Oettingen, W. F., Dunn, R. C., and Sharpless, N. E.: Toxicity and Potential Dangers of Aerosols and Residues From Such Aerosols Containing Three Per Cent DDT, Pub. Health Rep., supp. 183, 1945.
7. Neal, P. A., and von Oettingen, W. F.: The Toxicity and Potential Dangers of DDT to Humans and Warm-Blooded Animals, M. Ann. District of Columbia **4**: 15, 1946.
8. Wigglesworth, V. B.: Case of DDT Poisoning in Man, Brit. M. J. **1**: 517, 1945.
9. Hill, K. R., and Robinson, G.: Fatal Case of DDT Poisoning in a Child, With Account of Two Accidental Deaths in Dogs, Brit. M. J. **2**: 845, 1945.
10. Hill, W. R., and Damiani, R. C.: Death Following Exposure to DDT: Report of a Case, New England J. Med. **235**: 897, 1946.
11. Campbell, O. M. G.: DDT Poisoning in Man—A Suspected Case, Lancet **2**: 1178, 1949.
12. Case, R. A. M.: Toxic Effects of DDT in Man, Brit. M. J. **2**: 842, 1945.
13. Wright, C. S., Doan, C. A., and Haynie, H. C.: Agranulocytosis Occurring After Exposure to a DDT Pyrethrum Aerosol Bomb, Am. J. Med. **1**: 562, 1946.
14. White, W. C., and Sweeney, T. R.: The Metabolism of 2,2 bis (*p*-Chlorophenyl) 1,1,1 Trichloroethane (DDT) I. A Metabolite From Rabbit Urine, D 1 (*p*-Chlorophenyl) Acetic Acid; Its Isolation, Identification, and Synthesis, Pub. Health Rep. **60**: 66, 1945.
15. Neal, P. A., Sweeney, T. R., Spicer, S. S., and Von Oettingen, W. F.: The Excretion of DDT (2,2-bis [*p*-Chlorophenyl]-1,1,1-Trichloroethane) in Man, Together With Clinical Observations, Pub. Health Rep. **61**: 403 1946.
16. McGee, L. C.: Personal communication.

HIGH GASTROINTESTINAL OBSTRUCTION IN THE NEWBORN INFANT: A RADIOLOGICAL INTERPRETATION

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PERSISTENT VOMITING in the newborn period should be construed as evidence of intestinal obstruction until proved otherwise. Ladd and Gross[1] state that infants with intestinal or colonic atresia always have symptoms on the first day of life. If the cause of the obstruction is an intestinal stenosis most infants will show symptoms in the first week of life, with persistent vomiting the most marked symptom. Since the results of surgical intervention for these conditions in the newborn period are best when performed early, the establishment of the diagnosis of intestinal obstruction should be made as soon as possible. As Glover and McA. Barry[2] state, "unquestionably the most helpful aid in intestinal obstruction of the newborn that is available" is the plain or flat roentgenogram.

In a previous paper,[3] one of us discussed the radiological diagnosis of small bowel obstruction in infancy and childhood. It is the purpose of this paper to demonstrate the radiological findings of high gastrointestinal obstruction in the newborn period, and to emphasize the need for the earlier and more frequent use of the plain film of the abdomen as a screening procedure in newborn infants with persistent vomiting.

Wasch and Marek[4] have shown that gas appears within the proximal portion of the small intestine within the first hour of life. By the end of three hours, the entire small bowel contains gas, and air may also be seen in segments of large intestine. By the end of eight hours, there is a relatively large amount of gas in the small intestine as compared with the colon, and by twelve hours, the balance shifts so that the colon is more prominent. As previously shown, the normal small bowel in the infant appears radiographically as a formless, shapeless mass with a hazy, washed out appearance. (Fig. 1.)

In obstruction occurring in the duodenum or proximal portion of the jejunum, the plain film of the abdomen in the upright position reveals a large, distended, air-containing stomach and occasionally first portion of duodenum. A fluid level may be present depending on the amount of feedings previously given and the amount of vomiting. The remainder of the gut appears as an airless homogeneous haze. In cases where the obstruction is incomplete, as in a stenosis or congenital band, a few bubbles of air may be seen in the region of the duodenum or upper jejunum, with a greatly dilated duodenum and stomach above and an airless haze below. If such a condition is found, the diagnosis of high intestinal obstruction can be made and preparations for operation made

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without delay. Contrast media are not necessary to establish the diagnosis any further, and may, in fact, be dangerous because of the possibility of plugging the intestinal tract, making operation more difficult, and of vomiting and aspiration. Additional information concerning localization of the site of obstruction can be obtained by taking a plain film in the prone position. In this view, air may be visualized in the duodenum or proximal jejunum which was obscured by fluid in the erect position. It is also advisable to take films after decompression of the upper intestinal tract in order to determine the point beyond which air does not pass.

There is one condition in which symptoms of high intestinal obstruction may be associated with normally appearing intestinal shadows, namely, esophageal atresia with a tracheoesophageal fistula below the esophageal obstruction. In this case, although vomiting occurs early because of the esophageal atresia, air may enter the stomach and intestines via the tracheoesophageal communication.

The following case reports and their accompanying roentgenograms serve to illustrate the above remarks.

CASE REPORTS

CASE 1.—T. R., a white male infant, was born at the Beth-El Hospital on Sept. 23, 1947, exhibiting slight cyanosis and stigmata of mongolism. The cyanosis cleared and the infant did well until the fifth day of life when he began to vomit greenish material and the stools became scanty. The vomiting continued and there was an absence of stools. The infant was maintained on parenteral therapy and prepared for operation. At laparotomy, duodenal obstruction was found. The infant expired one day postoperatively. Post-mortem examination revealed a pin-hole stenosis at the junction of the second and third portions of the duodenum.

The tentative diagnosis of obstruction distal to the first part of the duodenum was made roentgenographically before operation. Plain films of the abdomen revealed a stomach which was large and distended with air. The duodenal cap was visualized and also contained air. There were no other air-containing intestinal loops in the abdomen. (Fig. 2.) Because of the lack of air in the small bowel in a child of this age, a diagnosis of obstruction immediately distal to the air-containing duodenal loop was made.

CASE 2.—M. T., a white female infant, was delivered at Beth-El Hospital on Sept. 12, 1949, after a thirty-seven week gestation, weighing 3 pounds, 14 ounces. The prenatal course was complicated by frequent vaginal bleeding. The infant's condition was good at birth and she thrived in the premature nursery, taking feedings well and having normal stools, until the sixth day when she began regurgitating part of her feedings. The next day the baby was vomiting greenish pea-soup material and passed currant-jelly blood clots per rectum. The abdomen was distended in the left-upper quadrant and a large cystic mass was felt here extending from left to right. This mass disappeared after decompression with a Levin tube. A tentative diagnosis of intestinal obstruction with volvulus and bowel necrosis was made. A laparotomy was performed and there was found a malrotation of the intestines with the cecum in the left-upper quadrant. There was an internal hernia of the proximal jejunum through a defect in the mesentery and a mesenteric thrombosis with infarction of the whole jejunum. These anomalies gave rise to intestinal obstruction at

the level of the ligament of Trietz. The bowel below this level was collapsed and contained no air.

Preoperative films of the abdomen revealed a small amount of air within the stomach and a small bubble of air in the small bowel. The remainder of the bowel showed a noticeable absence of air within its loops. (Fig. 3.) The air within the stomach along with an absence of air in the small bowel suggested a high intestinal obstruction. The small bubble of air in the small intestines suggested that the obstruction was partial.

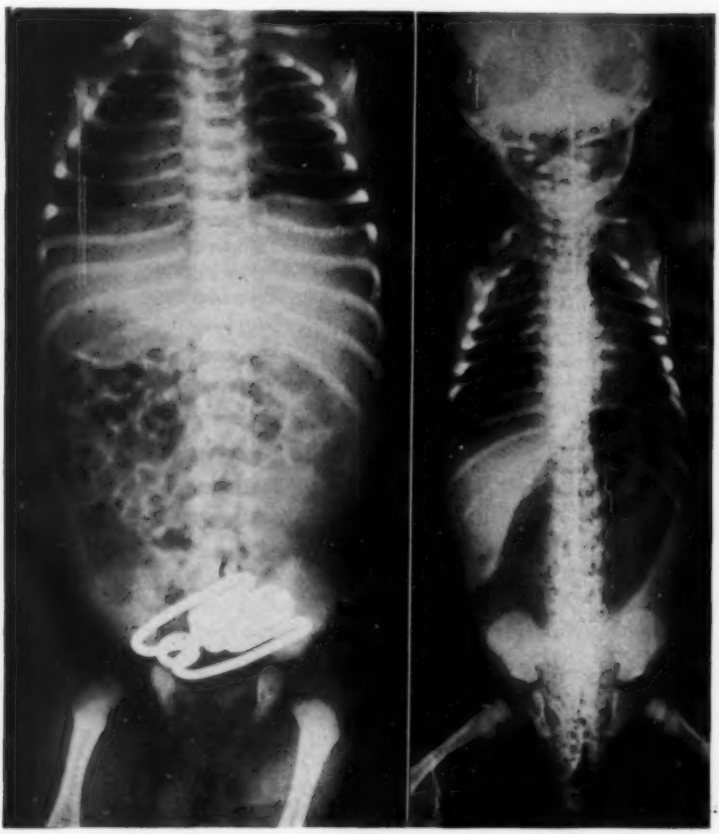

Fig. 1. Fig. 2.

CASE 3.—R. K., an 8-day-old female infant, was admitted to the Beth-El Hospital on Sept. 18, 1949, because of vomiting of two days' duration. She was born at this institution and did well during her five days' stay in the nursery, weighing 5 pounds, 14 ounces at birth and 6 pounds, 1 ounce on discharge. The day after discharge from the nursery she began to vomit all feedings, many in a projectile manner, with bile in the vomitus. On admission she was markedly dehydrated. There was no abdominal distention or masses. After roentgen studies and restoration of fluid and electrolyte balance a laparotomy

was performed. At operation, the findings consisted of a dilated stomach and first and second portion of the duodenum, with stenosis of the third portion of the duodenum and collapse of the rest of the small bowel. A gastrojejunostomy was done.

Preoperative radiographic examination of the abdomen in the erect position revealed a large stomach distended with air and showing evidence of a fluid level. A few small bubbles of air were seen in the upper portion of the small bowel. No air was seen in the remainder of small or large intestine. (Fig. 4.) In the prone position, the findings were essentially the same except that the duodenal cap was well visualized and distended with air. (Fig. 5.) Because of the large air-distended stomach and first portion of duodenum, and only a few bubbles of air in the proximal loops of small bowel, a diagnosis of incomplete high intestinal obstruction was made.

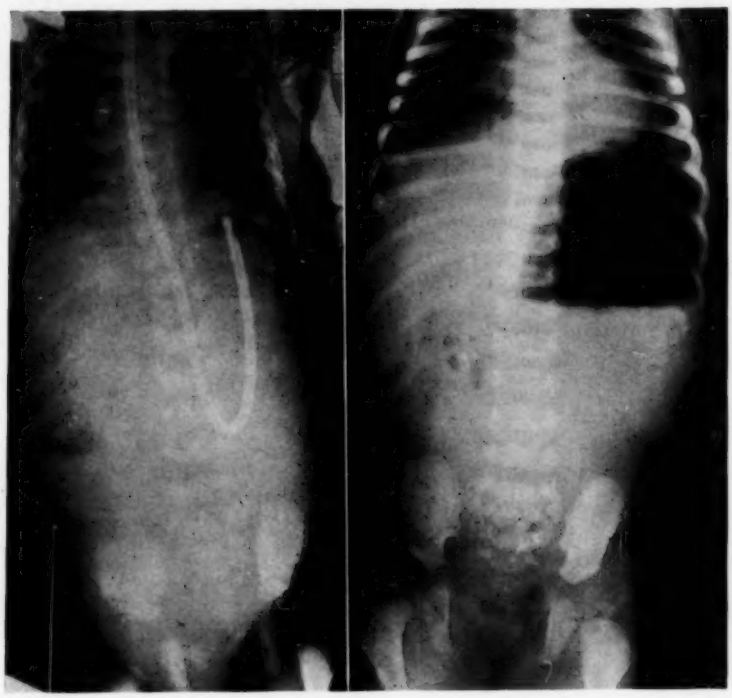

Fig. 3.

Fig. 4.

CASE 4.—T. L., a 5-day-old male infant, was admitted to Beth-El Hospital on Oct. 31, 1949, with a history of vomiting since birth and absence of stools for two days. Meconium had been passed during the first three days. The prenatal course was complicated by vaginal bleeding in the third month of pregnancy. On admission, the infant was dehydrated, had lost a pound from its birth weight of 5 pounds, 3 ounces, and vomited pea-souplike material. The abdomen was soft and no masses were present. A diagnosis of high intestinal obstruction was made and confirmed radiographically. After decompression

with Wangensteen suction and restoration of fluid and electrolyte balance, operation was performed. A dilated stomach and first and second portions of duodenum was found with collapsed intestines beyond the level of the third portion of duodenum. A diagnosis of duodenal stenosis was made and a duodenojejunostomy performed.

Preoperative radiographic films revealed a small collection of air in the fundus of the stomach and a few small bubbles of air in the right-lower quadrant suggesting a partial high intestinal obstruction. (Fig. 6.)

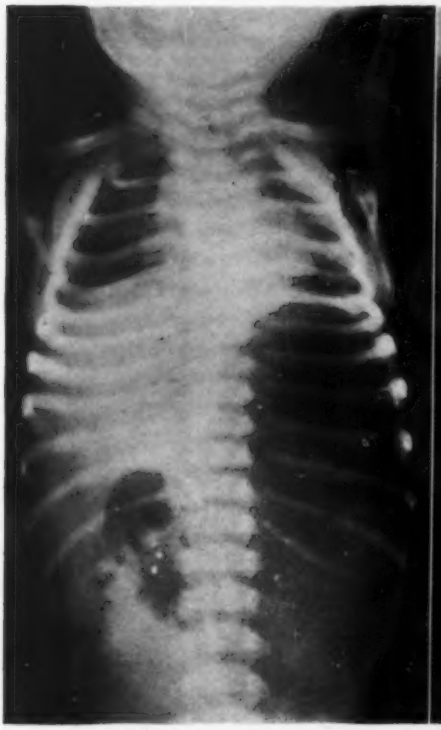

Fig. 5.

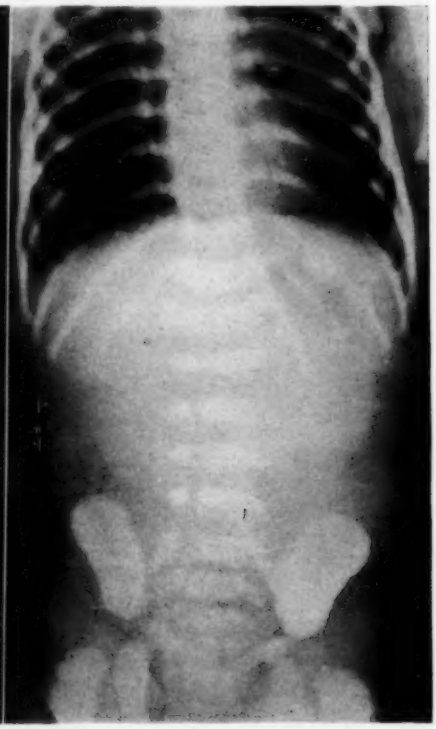

Fig. 6.

In order to localize the site of obstruction more precisely, the stomach was suctioned and air introduced. Repeat films showed air in the stomach and duodenal region, but no air beyond, except for the few bubbles in the right-lower quadrant previously mentioned, indicating that the obstruction was probably in the third portion of the duodenum. (Fig. 7.)

CASE 5.—R. K., a full-term male infant, was born at the Beth-El Hospital on July 13, 1947. At birth the infant was in poor condition and exhibited cyanosis. Râles were heard in all lung fields. There was a loud systolic murmur to the left of the sternum. A great deal of mucus was noted to be collecting in the baby's mouth. Clinically and roentgenographically a tracheo-esophageal

fistula was diagnosed. After preparation, the baby was operated upon on the fifth day of life and expired on the operating table. Autopsy revealed atresia of the upper part of the esophagus and a tracheo-esophageal fistula between the region of the carina and the lower end of the esophagus. Other congenital anomalies were hare lip, a cleft palate, tetralogy of Fallot, and congenital cyst of kidney.

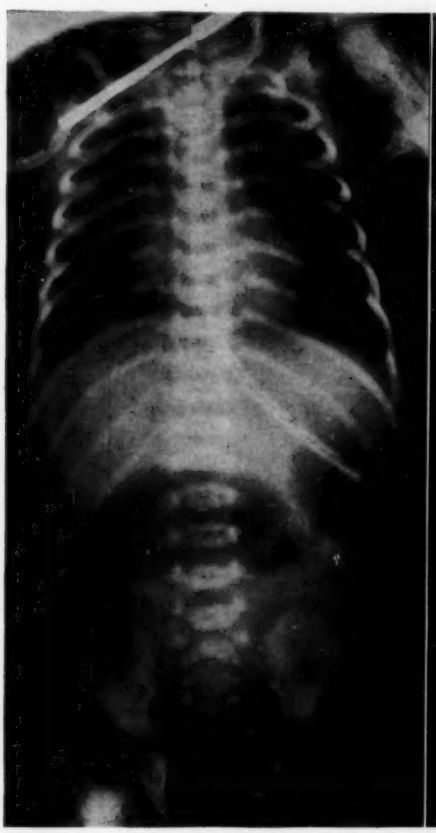

Fig. 7.

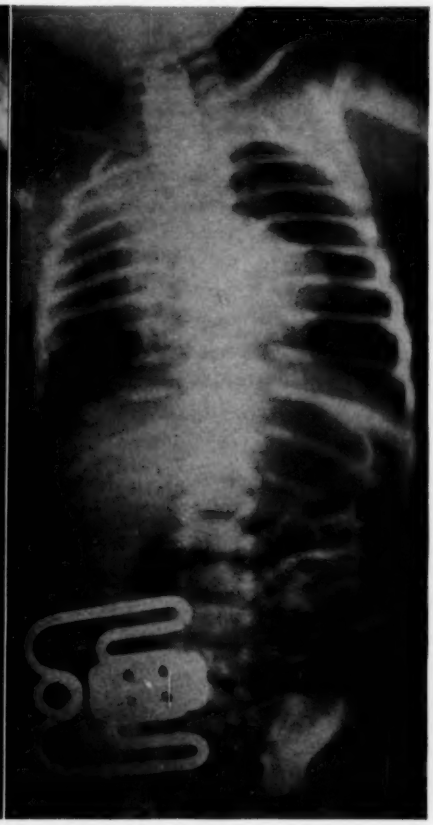

Fig. 8.

Radiographic examination of the abdomen revealed a normal distribution of air within the loops of bowel for an infant of this age. (Fig. 8.) In this case there was a high gastrointestinal tract obstruction (atresia of esophagus), but a normal air pattern in the abdomen because of the associated tracheo-esophageal fistula. This is the one exception where high gastrointestinal obstruction can be associated with normal gas patterns in the abdomen.

SUMMARY

1. The diagnosis of high gastrointestinal obstruction in the newborn infant by plain roentgenograms of the abdomen is discussed.

2. The earlier and more frequent use of this technique in infants with persistent vomiting is suggested.

3. It is suggested that plain films of the abdomen be taken in both the erect and prone positions before and after gastric suction for maximum information.

REFERENCES

1. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, 1948, W. B. Saunders Company.
2. Glover, D. M., and McA. Barry, F.: Intestinal Obstruction in the Newborn, Ann. Surg. 130: 480, 1949.
3. Storch, C., Redner, B., and Turin, R. D.: Small Bowel Obstruction in Infancy and Childhood, J. PEDIAT. 35: 366, 1949.
4. Wasch, M. G., and Marek, A.: The Radiographic Appearance of the Gastrointestinal Tract During the First Day of Life, J. PEDIAT. 32: 479, 1948.

Case Reports

CONGENITAL CHOLEDOCHUS CYST

Review of the Literature and a Case Report With One-Year Postoperative Follow-Up

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CHOLEDOCHUS CYST or congenital idiopathic cystic dilatation of the common bile duct is a condition which should be suspected in any infant or child who presents the triad of tumor, jaundice, and pain. The number of cases in the literature varies with the reporting authors, and postoperative follow-up examinations are seldom reported.

The condition is more common in women and in children, as is seen from an analysis of the collected cases in the literature. Judd and Greene[1] reviewed the literature in 1928 and were able to find only 64 cases prior to that time. Of these, 52 were female patients. The youngest case was in an almost full-term male fetus. In 1932, Zinninger and Cash[2] analyzed 82 cases, 68 of which were in female patients. All but 14 patients were under 30 years of age. Smith,[3] in 1942, collected 181 case reports from the literature and reported two more cases in adults. One year later, Shallow[4] reported a case along with a complete review of the literature which included 175 cases, 82 of which were those analyzed by Zinninger and Cash, and 44 of which were reported by Japanese authors. Seventy-seven per cent of these cases were in females and 76 per cent of them were below 25 years of age. Kelsey,[5] in reporting a case in a 4-year-old white girl in 1947, was able to find 71 case reports in children. Two of these were in the American pediatric literature, being reported by Gross[6] and by Berkley.[7] Only two cases were recorded in the literature between Kelsey's report in August, 1947, and June, 1948. Both of these were in adults and were reported by Fleming[8] and Keeley.[9] The total number of cases in the literature probably does not exceed two hundred.

Several theories have been advanced as to the cause of congenital choledochus cyst. Among these are valviform reduplication of the wall of the cyst with closure of the duct, abnormal course of the common bile duct through the wall of the duodenum, weak muscular tissue of the duct, congenital narrowing of the duct as it enters the duodenum, adhesions, and syphilis. Gross[6] believes the first two of these are the most likely causes.

Choledochus cysts vary greatly in size, some of them being several centimeters in diameter. The terminal portion of the common duct is seldom, if ever, involved. The cyst wall is composed of dense connective tissue and there is usually a thickened rather than a thin wall. Elastic fibers and smooth muscle may be present but glands are rarely found. Bile is found within the cyst the lining of which may or may not have epithelium. The gall bladder is usually normal in size. The liver shows changes consistent with the degree of obstruction, some of the more frequently mentioned changes being

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hepatomegaly and cirrhosis. Cholangitis is not uncommon, and splenomegaly and ascites may occur. There may be a displacement of portions of the gastrointestinal tract by the cyst.

Almost all of the reported cases have had at least two, and usually all three, of the previously mentioned triad of salient features. Jaundice, usually intermittent, is the most common symptom, whereas a tumor is the most significant diagnostic criterion. The latter is especially diagnostic when it is a palpable cyst in the right-upper quadrant of the abdomen in a young female, according to Judd and Greene.[1] Pain usually varies in severity, is irregular, and most often occurs in the right-upper quadrant of the abdomen. Other signs and symptoms are fever, pruritus, clay-colored stools, anorexia, weight loss, vomiting, diarrhea, and dark urine. The spleen and liver may be enlarged, and there may be distention of the superficial veins of the chest and abdominal wall.

Some of the more common erroneous diagnoses made in patients with choledochus cyst are echinococcus cyst, pancreatic tumor, stone in the common duct, retroperitoneal cyst or sarcoma, cholecystitis or cholelithiasis, hydrops or enlarged gall bladder, cyst of the liver, and mesenteric cyst.

Preoperative diagnosis has not been frequently made in the past. In the 175 cases reviewed by Shallow,[4] choledochus cyst was diagnosed in only 8.6 per cent. The correct diagnosis was made only three times preoperatively in the 82 cases which Zinninger and Cash[2] analyzed. Swartley[10] emphasizes that the preoperative suspicion of the condition "makes dealing with it in the abdomen more effective, lessens mortality and improves results." Shallow[4] found a 36 per cent over-all mortality where the preoperative diagnosis was correct or suspected as compared to a 62 per cent mortality where the diagnosis was not made or was incorrect. Laboratory studies may or may not be of value in making a diagnosis. X-rays of the abdomen, gastrointestinal series, and urinary tract visualizations are of great value.

The mortality is 100 per cent in cases without surgical treatment. Those aspirated alone and those excised with or without anastomosis also bear a 100 per cent mortality. The over-all mortality in Shallow's review,[4] regardless of treatment, was 58 per cent. Gross[6] reports a mortality of 69 per cent in children. However, with primary anastomosis of the biliary tract and intestines, the mortality was only 9 per cent.

Choledochoduodenostomy is the treatment of choice, leaving the cyst wall intact. Keeley[9] obtained good results in an adult with a Roux en Y anastomosis. External drainage of the cyst and excision of the cyst are not advisable in that ascending infection and uncontrollable hemorrhage usually result in death of the patient.

One of the most common complications reported throughout the literature is cirrhosis of the liver. Other postoperative complications are ascending cholangitis of recurrent nature, hepatitis, liver abscess, and peritonitis.

CASE REPORT

K. S., aged 4 months, was admitted to the hospital Aug. 31, 1948, with the chief complaint "vomiting." The mother had had an uneventful ante-partum course and delivery was spontaneous and normal. The baby was apparently normal at birth. However, the meconium stools were followed by clay-colored stools. On the fifteenth day of life the mother first noted a yellow tinge of the skin and scleras. Vomiting after feedings became a prominent feature, and the abdomen began to enlarge. A physician saw the baby at this time and palpated a mass in the right-lower quadrant of the abdomen. He also found the mother to be Rh negative and the father Rh positive. The baby was

given hip injections of the father's blood and placed on antispasmodic therapy before feedings.

The vomiting, which was never projectile, became less severe. The icterus increased in intensity and the baby began to lose weight. Two weeks prior to admission to the hospital, the mother noted a mass in the right-upper quadrant of the abdomen just beneath the costal margin.

The family history and social history were noncontributory.

Physical examination revealed a fairly well-nourished white female infant, in no apparent distress, who weighed 5 kilograms. Temperature, pulse, and respiration were normal. Salient features in the physical examination were: marked generalized icterus of the skin, icteric scleras and mucous membrane of the mouth, distention of the superficial veins of the lower chest anteriorly and of the abdomen, distended and tympanitic abdomen with shifting dullness, and large cystic mass in the right-upper and lower abdominal quadrants (Fig. 1) which did not move with respiration. The lower border of the liver and the spleen were not palpable. It was thought that the baby had an obstruction of the common bile duct due to a congenital anomaly. Congenital choledochus cyst was first among the preoperative diagnoses.

Fig. 1.—Preoperative photograph of K. S., aged 4 months, showing abdominal mass which proved to be a choledochus cyst.

Laboratory Data.—On admission the hemogram revealed only a hypochronic anemia. The urine was amber colored, and urinary urobilinogen was positive through a 1:100 dilution. Stools were clay colored. Clotting time was 2 minutes, 36 seconds. Blood group was O, Rh positive. Total serum protein was 5.3 Gm. per cent. Cephalin flocculation was 3-plus at twenty-four hours. Formol-gel test was negative. Thymol turbidity was 11 units.

Chest x-ray and intravenous pyelograms were reported as normal. An upright x-ray of the abdomen revealed a mass occupying the right-upper and lower quadrants, displacing the intestines to the left, and reported as consistent with a grossly enlarged liver.

The baby was maintained preoperatively on adequate oral feedings, vitamin K (Synkavite), choline chloride, and one transfusion of type O, Rh-positive whole blood. One week after admission, an operation was performed by one of us (C. E. H.). The perintoneal cavity contained a small amount of straw-colored fluid. A large cystic mass occupied the entire right side of the abdomen, displacing the viscera to the left (Fig. 2). A peritoneal veil which completely covered the mass contained numerous blood vessels. The gall bladder was normal in size and position. The liver was normal in size and had a nutmeg appearance. The spleen was not enlarged. Needle aspiration of the cyst yielded 850 c.c. of bile. A side-to-side anastomosis of the cyst and the duodenum was performed (Fig. 3). Immediate postoperative condition was good.

Subsequently, the baby was maintained on calculated amounts of calories, protein, salt, and fluids, and she received vitamin K, penicillin, and choline chloride. She had temporary edema and oliguria, and hematemesis and melena on one occasion.

Laboratory data during this time revealed a carbon dioxide combining power of 65 volumes per cent, nonprotein nitrogen of 66.5 mg. per cent, blood urea of 48.4 mg. per cent, and creatinine of 0.95 mg. per cent. Total serum protein was 3.43 Gm. per cent, serum albumin 1.87 Gm. per cent, and serum globulin 1.56 Gm. per cent. There was a mild hypochromic anemia, and the white cell count was 14,000 with a normal differential count. A catheterized urine specimen was amber colored. An increased amount of intravenous protein was given, and the baby's condition improved markedly.

Fig. 2.—Photograph at operation showing relationship of choledochus cyst to surrounding structures. *A*, liver; *B*, stomach; *C*, transverse colon; *D*, choledochus cyst.

The first yellow-brown stool appeared on the second postoperative day. The icterus of the skin, sclerae, and mucous membrane of the mouth decreased rapidly. Oral feedings were instituted and she gained weight well. Before her dismissal from the hospital, the cephalin flocculation was 2-plus in twenty-four hours, red blood count was 4.25 million, hemoglobin 80.6 per cent (12.5 Gm.). Except for low-grade fever the first two days and the seventh day postoperatively, the temperature remained normal. She was dismissed from the hospital one month after admission, in satisfactory condition.

She was seen again in the out-patient department two weeks later. Her weight was 5 kilograms. She was eating well, having stools of normal color and consistency, and was not vomiting. There was no clinical jaundice. The lower border of the liver was smooth and nontender, being palpated 2.5 cm. below the xiphoid, 4 cm. below the right costal margin in the midclavicular line, and 2.5 cm. below the right costal margin in the anterior axillary line. The spleen was not palpable.

During the following five months, she had roseola and several episodes of acute tonsillitis. Laboratory data on March 4, 1949, was as follows: thymol turbidity 13.5 units, cephalin flocculation 4-plus in twenty-four hours, formol-gel negative, total serum protein 6.4 Gm. per cent, serum cholesterol 152 mg. per cent, icterus index 24 units, and delayed direct van den Bergh.

She was readmitted to this hospital on June 29, 1949, at 14 months of age, with the chief complaints of abdominal distention and fever. Her weight was

8.5 kilograms. The abdominal distention had progressively increased for two weeks prior to admission, causing moderate respiratory difficulty. There was a 2 pound weight gain during this time. For one week prior to admission she had had tonsillitis and was treated with penicillin. The urine had been a little darker in color than usual, but the stools were normal in color and consistency.

Physical examination on this admission revealed a moderately ill baby with fever, irritability, grunting cry, and large abdomen. Heart rate was 160, respiratory rate 35. There was no clinical jaundice. The lips were slightly pale. Pharynx and tonsils were hyperemic. There was a soft apical systolic murmur. The abdomen was markedly distended, a fluid wave was elicited, and there was shifting dullness. The lower border of the liver was hard and irregular to palpation and was 4 fingerbreadths below the right costal margin in the midclavicular line, 5 fingerbreadths below the xiphoid, and 3 fingerbreadths below the left costal margin in the midclavicular line. The spleen was firm and had a sharp border, being palpated 3 fingerbreadths below the left costal margin in the anterior axillary line.

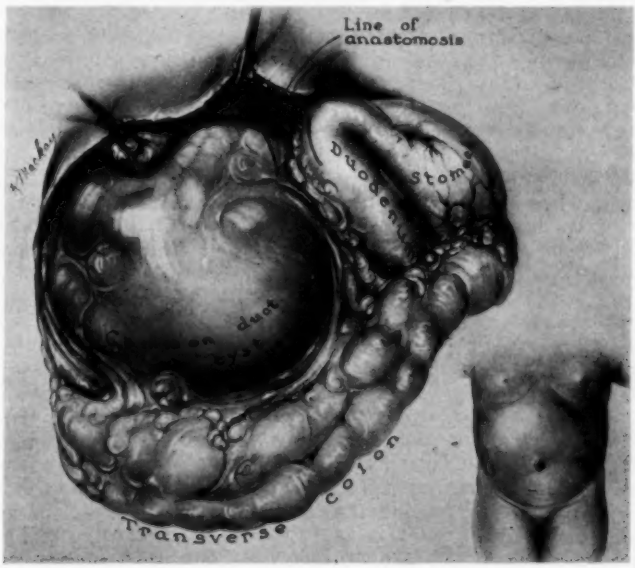

Fig. 3.—Artist's sketch of findings at operation to show site of anastomosis of choledochus cyst and duodenum. Also, preoperative sketch to show size of abdominal mass.

Laboratory Data.—Laboratory data was as follows: Hemogram revealed only a hypochromic anemia. Urine was essentially normal. Prothrombin time was 52 per cent of normal. Cephalin flocculation was 3-plus at twenty-four hours, 4-plus after forty-eight hours. Total serum protein was 6.01 Gm. per cent (albumin 3.32 Gm. per cent, globulin 2.69 Gm. per cent).

An upright x-ray of the abdomen showed only hepatomegaly.

The consensus was that she had a subsiding tonsillitis, hypochromic anemia, and portal hypertension on the basis of an intrahepatic block. She improved following treatment with penicillin, one transfusion of whole blood, and symptomatic therapy. The abdominal distention decreased considerably.

It was proposed that at a later date she should have a tonsillectomy, liver biopsy, and possibly a portal-caval shunt. She was discharged from the hospital three days after admission.

Her third hospital admission was Oct. 25, 1949, thirteen months after the first admission. She was well nourished and had no clinical jaundice. Stools and urine had been normal. Developmental history was normal. The liver edge was palpable 2 fingerbreadths below the right costal margin in the midclavicular line and was firm, somewhat nodular, but nontender. The spleen was not palpated. Bleeding time was 6½ minutes, coagulation time was 4 minutes. Tonsillectomy and adenoidectomy were performed. The postoperative course was uneventful, and she was discharged home in satisfactory condition.

SUMMARY

Congenital choledochus cyst, although a rare condition, should be suspected in any individual with jaundice, abdominal tumor, and pain.

A partial review of the literature is presented, along with a discussion of the cause, pathology, signs and symptoms, diagnosis, mortality, treatment, and complications of the condition.

A case in a 4-month-old white female is reported, with a one-year postoperative follow-up.

REFERENCES

1. Judd, E. S., and Greene, E. I.: Choledochus Cyst, Surg., Gynec. & Obst. **46**: 317-324, 1928.
2. Zinninger, M. M., and Cash, J. R.: Congenital Cystic Dilatation of Common Duct, Arch. Surg. **24**: 77-105, 1932.
3. Smith, B. C.: Cyst of the Common Duct, Arch. Surg. **44**: 963-983, 1942.
4. Shallow, T. A., Eger, S., and Wagner, F., Jr.: Congenital Cystic Dilatation of the Common Bile Duct, Ann. Surg. **117**: 355-386, 1943.
5. Kelsey, W. M.: Idiopathic Dilatation of Common Duct in Childhood, J. PEDIAT. **31**: 211-212, 1947.
6. Gross, R. E.: Idiopathic Dilatation of the Common Bile Duct in Children, J. PEDIAT. **3**: 730-755, 1933.
7. Berkley, H. K.: Idiopathic Dilatation of the Common Bile Duct in Childhood, J. PEDIAT. **14**: 79-82, 1939.
8. Fleming, R. J.: Cyst of Common Bile Duct in Case of Pregnancy of Eight Months, South African M. J. **21**: 778-782, 1947.
9. Keeley, J. L.: Congenital Cystic Dilatation of Common Bile Duct, Arch. Surg. **56**: 508-515, 1948.
10. Swartley, W. B.: Choledochus Cyst, Ann. Surg. **118**: 91-96, 1943.

TRICHOBEZOAR IN A FOUR-YEAR-OLD CHILD

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TRICHOBEZOAR is a very rare condition in children under 5 years of age. Among the various bezoars, the trichobezoars are the most common.[1] Numerous cases have been recorded but we are unable to find more than five such cases in children of 5 years of age or younger.[2-6]

Bezoars are the result of ingestion of nonabsorbable materials which fail to pass through the pylorus. Hair or other objects become adherent and gradually form a large mass in the stomach. If composed of hair they are known as trichobezoars and, if composed of vegetable fibers, as phytobezoars. In the case of trichobezoars one can usually obtain a history of eating hair which came from the patient's head or from blankets and clothing. This habit is usually acquired early in life. Most cases become symptomatic only after a considerable lapse of time. The condition is much more common in girls than in boys, presumably due to the longer hair worn by girls.

Due to the insensitivity of the gastric mucosa, symptoms are produced only when complications arise.[7] Pyloric obstruction is the most common complication producing nausea, vomiting, anorexia, and malnutrition. Less commonly encountered complications are perforation, hemorrhage, and ulceration. Associated with these various symptoms is often an abnormal craving for unusual foods and other objects. Many cases occur in mentally ill patients and Maes[8] believes that, if a psychic factor is present, the patient will begin eating hair during convalescence from any illness or necessary operative procedure.

Epigastric masses are commonly present in these cases since bezoars may reach sizable proportions. Occasionally hair may be demonstrated in the vomitus or a portion of the hair ball may pass through the intestinal tract. Sometimes a part of the hair ball may lodge in the bowel producing intestinal obstruction.

Radiographic study of the upper gastrointestinal tract is especially helpful in establishing a diagnosis. In the fluoroscopic examination the barium is seen to enter the cardiac end of the stomach then spread over the surface of the bezoar leaving a central empty space. This empty space may even give the impression of an air bubble.[1] An examination of the six-hour film is of special value as it usually demonstrates a central, dark-appearing space surrounded by barium.[9] The gastroscopic examination for direct visual information is also very helpful.[10]

The treatment of bezoars is surgical removal to prevent gastric complications and intestinal obstruction, and to improve the nutritional state of the patient. After removal, precautional measures including psychotherapy, if indicated, should be instituted to prevent recurrences.

CASE REPORT

S. H., a 4½-year-old girl, was admitted to the Children's Hospital on May 22, 1949. Her birth and early development had been normal. The chief admission complaints were vomiting, pulling out hair, and nervousness. During the preceding eighteen months the patient had been irritable and restless. One year previously the child lost her hair from an undetermined cause. As the hair growth returned the parents noted that the child pulled out most of

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Fig. 1.

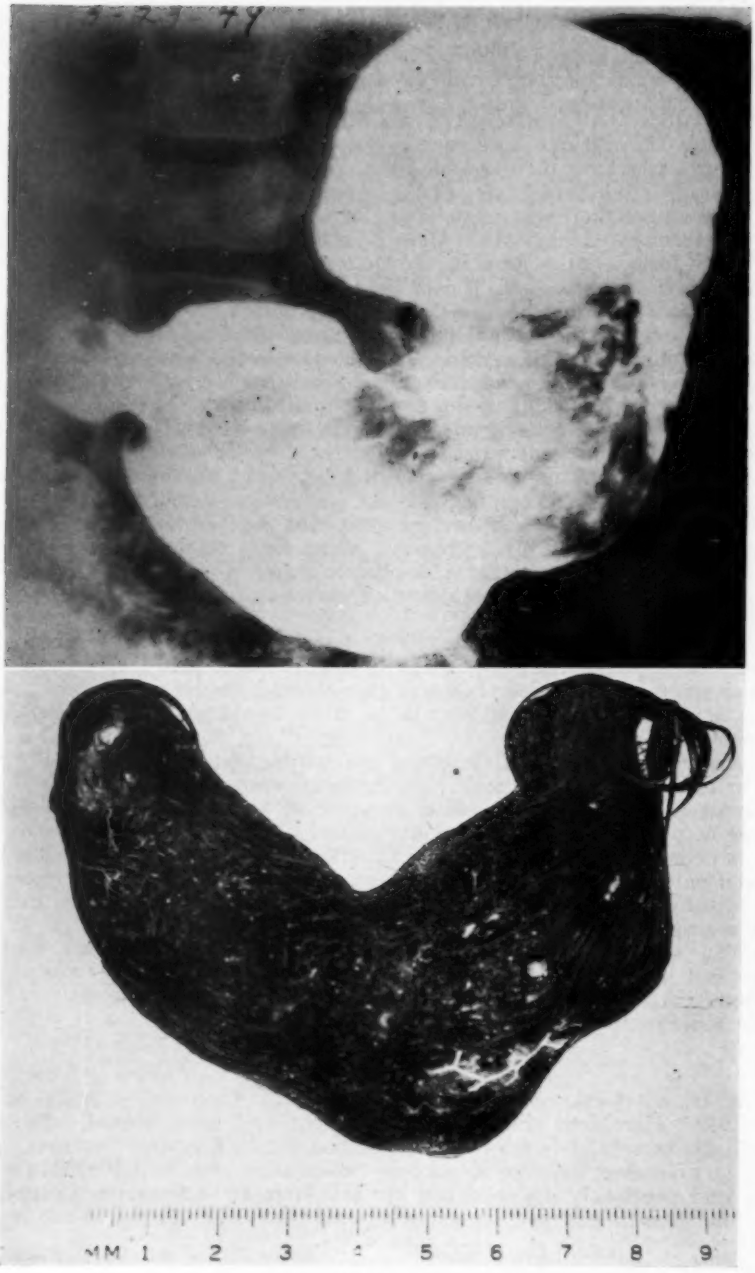

Fig. 2.

her hair. Vomiting attacks had commenced about twenty months previously, were irregular in occurrence, and were not associated with any known factor. The parents had not seen any evidence of bile in the vomitus. The patient belched considerably and the eructations had a vrey foul odor. There was anorexia but no weight loss or bleeding episodes were noted.

Physical examination revealed a well-developed, well-nourished girl with extremely short, irregular hair. In the left epigastrium was a mass extending from the midline to the left for 4.0 cm. and upward under the subcostal margin. The mass was freely movable and nontender. No other significant findings were noted.

Laboratory Data.—The urine was negative. There were 4,190,000 erythrocytes; 8,400 leucocytes, with 54 per cent granulocytes, and 46 per cent lymphocytes; the hemoglobin was 12.5 Gm. Kahn test was negative.

Radiological Report: The stomach showed a filling defect, which was irregularly oval in shape and measured 4.0 × 7.0 cm. in size. It appeared to be freely movable within the stomach. The stomach emptied well and the upper gastrointestinal tract showed no other abnormality.

Clinical Impression: A freely movable, filling defect was in the stomach which, with the patient's history, most likely represented a trichobezoar. (Fig. 1.)

On May 27, 1949, a gastrostomy was performed under ether anesthesia. A large mass composed of matted hair which almost completely filled the stomach was removed. The intestine was examined throughout its length and no masses were present. The postoperative convalescence was uneventful.

The specimen weighed 92.0 Gm. It was firm and made up of strands of hair arranged longitudinally with some in a circular pattern. The configuration was that of a stomach with its greater curvature measuring 19.0 cm., its lesser curvature 10.0 cm., and its diameter 4.0 cm. (Fig. 2).

During the postoperative convalescence period psychometric studies demonstrated that the child had normal intellectual facilities. A fear of her father and men in general was present and it was the opinion of the analyst that psychotherapy was indicated. Since discharge from the hospital the child has had no difficulties, eats well, and is gaining weight. Her parents have observed no further ingestion of hair.

SUMMARY

A brief discussion of trichobezoar with a rare case occurring in a 4½-year-old child has been presented.

REFERENCES

1. Camp, J. D.: Phytobezoar in the Stomach, Am. J. Roentgenol. **23**: 413-414, 1930.
2. Doolin, William: A Case of Hair-Ball of the Stomach, Irish J. M. Sc. **11**: 641-642, 1926.
3. Smith, Jean: Hair-Eating and Pica in Children, Brit. J. Child. Dis. **28**: 282-289, 1931.
4. Bruce, G. Gordon: A Case of Hair-Ball of the Stomach and Duodenum in a Child of Three and One-half Years, Brit. J. Surg. **23**: 855-857, 1935-36.
5. Schwartzman, Joseph: Trichobezoar, J. PEDIAT. **11**: 691-696, 1937.
6. Graberger, von Gosta: Über einen Fall von Trichobezoar, Acta radiol. **25**: 504-506, 1944.
7. Christopher, Frederick: Foreign Bodies of the Stomach, Textbook of Surgery, ed. 5, Philadelphia, 1949, W. B. Saunders & Company, p. 956.
8. Maes, Urban: Bezoars, With the Report of Additional Cases of Phytobezoar, Ann. Surg. **88**: 685-692, 1928.
9. Holmes, G. W., and Ruggles, H. E.: Roentgen Interpretation, ed 4, Philadelphia, 1931, Lea & Febiger.
10. Patterson, Cecil O., and Rouse, Milford O.: Foreign Bodies in the Stomach Observed Through the Gastroscope, Report of Five Cases, Texas State J. Med. **36**: 238-241, 1940.

ATRESIA OF THE PULMONARY ARTERY WITH INTACT INTERVENTRICULAR SEPTUM

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FOLLOWING the report of the first successful ligation of a patent ductus arteriosus by Gross and Hubbard[1] in 1939, interest was stimulated in the congenital defects of the heart and great vessels. Great impetus was given to the study of these defects by the reports of Crafoord[2] on the surgical correction of coarctation of the aorta and of Blalock and Taussig[3] on the surgical amelioration of pulmonary stenosis and atresia. In view of the general interest in congenital heart disease and of the rarity of the lesion presented by our patient, the following case is reported.

CASE REPORT

A 3½-month-old male infant was admitted to The Children's Hospital with the chief complaint of cyanosis since birth. The child was born at term without complications. Birth weight was 5 pounds, 14 ounces. There was little difficulty in resuscitation, although it was noted that the infant remained cyanotic even in oxygen. He remained in the hospital two weeks and was then discharged. His course at home had been good except for constant cyanosis of the nail beds and over the bridge of the nose. Cyanosis was noted to deepen with crying.

During the night before admission following an episode of crying he turned pale and cold and his eyes rolled back in his head. He improved slowly over a period of one hour, but on the afternoon of admission a similar episode recurred. The child was referred to Children's Hospital for a complete study.

Family History.—The child's mother, aged 24 years and his father, aged 20 years, were both living and well. There had been no other pregnancies.

Feeding History.—The child took his formula well and was started on cereals and vegetables at age 3 months. Cod liver oil and orange juice had been given in adequate amounts.

Physical Examination.—On admission the child was noted to be intensely cyanotic but did not appear acutely ill. He weighed 9 pounds, 3 ounces. The left eardrum was injected and there was a mucopurulent secretion in the nose. Examination of the lung fields revealed scattered rhonchi but no râles or dullness. There was no pericardial shock or thrill; the left cardiac border was percussed to the anterior axillary line in the fourth and fifth interspaces. The rate was 180 per minute. Rhythm was regular and no murmurs were heard. Blood pressure reading was not attempted. The liver, spleen, and kidneys could not be palpated.

Initial laboratory examination revealed a red blood cell count of 5.68 million per cubic millimeter, and a hemoglobin of 18 Gm. per cent. The white blood count was 10,100 per cubic millimeter with a differential count of 62 per cent neutrophils, 36 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophils. Urinalysis revealed a 2-plus albumin with from 3 to 6 white blood cells per high power field and a few granular and hyalin casts.

Electrocardiogram revealed high P waves in the standard leads and evidence of right ventricular strain. Fluoroscopic and teleroentgenographic

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studies revealed marked enlargement of the left ventricle, questionable enlargement of the right ventricle, absence of the pulmonary artery, and evidence of dextroposition of the aorta. The lung fields appeared abnormally clear.

The clinical impression at this time was tetralogy of Fallot.

Course in the Hospital.—The child was begun on penicillin for his otitis media and seemed to be progressing nicely until the third day of hospitalization when moist râles were noted on auscultation of the bases of the lungs. The cardiac rate was noted to have increased to approximately 200 and the liver became palpable 3 cm. below the costal margin. On the fourth hospital day the infant was digitalized and following this the cardiac rate was reduced to 130 per minute. The liver remained palpable and the râles were audible over the lung bases. Following the onset of failure the child's course in the hospital was gradually downhill despite oxygen therapy and digitalis. He expired twelve days after admission.

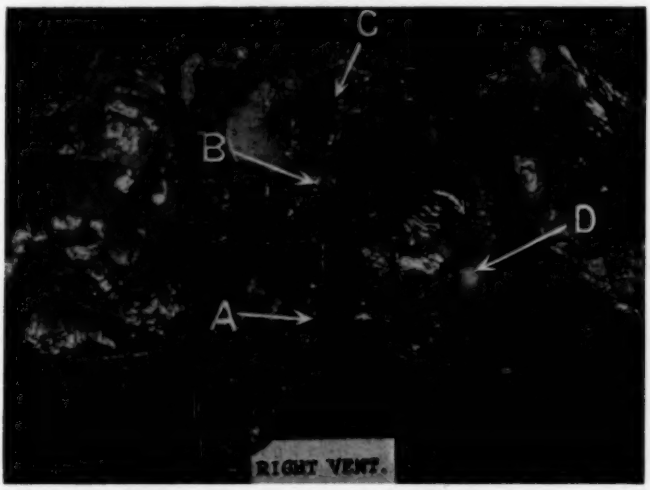

Fig. 1.—Gross specimen of the heart and great vessels showing: *A*, the organizing mural thrombus in the right ventricle; *B*, the base of the pulmonary artery; *C*, patent ductus arteriosus; and *D* atheroma, anterior descending branch of the left coronary artery.

Results of Post-Mortem Examination.—The necropsy findings of interest were limited to the heart and great vessels. (Fig. 1.) The heart was markedly enlarged, compressing and displacing the left lung laterally and impinging on the right lung. The right and left ventricles and the right auricle were markedly distended. Both ventricular walls measured 5 mm. in thickness. The coronary arteries were large. Midway down the anterior wall of the ventricular septum there was a 1.0 cm. segment of the anterior descending branch of the left coronary artery which was involved in a golden atheromatous change. Here the lumen was pin-sized. The tricuspid valve was normal but in the right ventricle there were lobulated mural thrombi undergoing organization between the folds of the papillary muscles. No pulmonary artery orifice was demonstrable either by dissection or by injection of water under syringe pressure. Dissection failed to reveal any vestigial pulmonary cusps.

There was a 1.0 cm. patent foramen ovale in the interatrial septum. No interventricular septal defect was present and the aorta arose in its normal

location. The ductus arteriosus was widely patent and offered the only channel for blood to the lungs. This same blood, by retrograde flow, had filled and dilated the pulmonary artrey from the ductus orifice to the atresia of the pulmonary orifice at the base of the heart.

The course of blood flow (Fig. 2) was into the right auricle, through the tricuspid orifice, and stagnation in the right ventricle; through the foramen ovale into the left auricle. In the left auricle venous blood and a small amount of oxygenated blood from the lungs were mixed and pumped out of the aorta. At the ductus, a fraction of this blood was shunted through the ductus arteriosus for aeration by the lungs while the remainder of the mixture entered the systemic circulation.

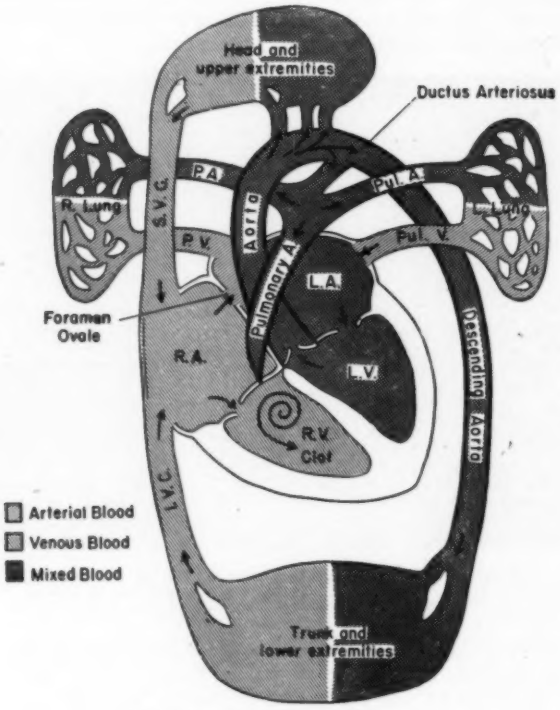

Fig. 2.—Circulation diagram.

DISCUSSION

A review of the literature has failed to disclose a detailed report of a similar lesion. Maude Abbott[4] reported ten cases of pulmonary atresia with closed ventricular septum and of these only one had an associated hypertrophy of the right ventricle. Nine had a patent ductus arteriosus and ten had an interauricular septal defect. The age range was 6 days to 20 years with a mean of 1¾ years. Eliminating the case of the 20-year-old, the average age at death was 2¼ months. All were cyanotic. Of the ten cases presented only one could have been similar to ours. No reference to such a case

is presented in the text. Review of subsequent case reports[5] reveals the more common findings of a small or aplastic right ventricle with atresia and hypertrophy of the right ventricle with stenosis.

The cause of this defect is difficult to explain. Abbott suggested endocarditis. In the opinion of Rossman[5] who wrote that stenosis is associated with hypertrophy of the right ventricle and atresia with aplasia, it would seem that our patient originally had a stenosed pulmonary orifice which allowed the right ventricle to develop normally and to hypertrophy. The orifice then closed off either shortly before birth or shortly thereafter, trapping the blood in the right ventricle. This stagnation caused clotting and the formation of mural thrombi. With the added strain on the left ventricle of having to pump blood to both circulations, dilatation and hypertrophy of the left ventricle occurred.

SUMMARY

1. A case is presented with the clinical picture of tetralogy of Fallot.
2. At necropsy an atresia of the pulmonary orifice with a closed interventricular septum was discovered.
3. Only one possibly similar case was discovered in the literature.
4. A brief explanation of the pathologic findings is suggested.

REFERENCES

1. Gross, R. E., and Hubbard, J. P.: Surgical Ligation of Patent Ductus Arteriosus: Report of First Successful Case, J. A. M. A. **112**: 729-731, 1939.
2. Crafoord, C., and Nylin, G.: Congenital Coarctation of Aorta and Its Surgical Treatment, J. Thoracic Surg. **14**: 347-361, 1945.
3. Blalock, A., and Taussig, H. B.: Surgical Treatment of Malformations of the Heart in Which There Is Pulmonary Stenosis or Pulmonary Atresia, J. A. M. A. **128**: 189-202, 1945.
4. Abbott, Maude: Atlas of Congenital Cardiac Disease, New York, 1936, American Heart Association.
5. (a) Blackford, L., and Parker, F. P., Pulmonary Stenosis With Bundle Branch Block, Arch. Int. Med. **67**: 1107, 1941; (b) Rossman, J. I., Congenital Atresia and Stenosis of Great Cardiac Vessels, Am. J. Dis. Child. **64**: 872, 1942; (c) Garrison, R. E., and Feldt, R. H.: Congenital Pulmonary Stenosis With Closed Cardiac Septa, Am. Heart J. **24**: 685, 1942; (d) Rossman, J. I.: A Rare Congenital Cardiac Anomaly: Cor Biloculare, Transposition and Atresia of the Pulmonary Artery, Proc. Inst. Med., Chicago **14**: 265, 1942; (e) Auerbach, S. H., and Harper, H. T., Jr.: Congenital Pulmonary Stenosis With Closed Interventricular Septum, Am. Heart J. **34**: 131, 1947; (f) Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary Stenosis With Intact Interventricular Septum, Am. Heart J. **30**: 491, 1945; (g) Rutledge, D. I.: Approach to the Diagnosis of the Common Types of Congenital Heart Disease, J. A. M. A. **141**: 1290, 1949; (h) Mannheimer, E.: The Diagnostic Value of Cardiac Catheterization in Isolated Pulmonary Stenosis and Large Interventricular Septal Defects, Arch. Dis. Child. **24**: 264, 1949.

Medical Progress

CHANGING PHILOSOPHIES IN CLEFT PALATE MANAGEMENT

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IT IS interesting and amusing to page through early medical journals. In contrast with present-day scientific reticence to make positive commitments, excerpts from periodicals of 100 years ago provide uniquely complete and infinitely varied answers to most medical problems. For congenital deformities, such as harelip and cleft palate, the literature runs the gamut of all possible and impossible etiological factors, all with the same degree of ultimate authority. A case report made in 1841, illustrates one popular theory. The author describes in detail a complete lip-jaw-palate cleft in a 6-week-old boy "a fine healthy specimen, notwithstanding his deformity." Under the heading of "etiology," the author tells us that the mother, while pregnant, frequently sat by a window which faced a circus across the street. Unfortunately, her view permitted her to look at a tent decorated with a large, brightly colored picture of a grinning hippopotamus, his mouth partly open and the gleaming yellow tusks protruding from it. Exposure to such a view, the author concluded, indubitably was the cause of the cleft palate in the offspring. The work of the last one hundred years has produced considerably more erudite etiologies for cleft palate and harelip. Theories of mutation of genes, transmigration of tissue, epithelial bridging, heredity, obscure blood dyscrasias, and nutritional disturbances all have their proponents and the controversy still exists. On the embryonal nature of the cleft there is general agreement. Cleft lip results from the lack of fusion of the medial and lateral nasal processes and the maxillary process. Cleft palate occurs when there is lack of fusion of the palatine processes with each other and the nasal septum. (Fig. 1.) The critical time period is between the eighth and eleventh week of fetal life.

Since there is controversy over the cause of cleft lip and cleft palate, it is no wonder that contemporary therapeutic aims and techniques are so diverse. Management of the problem in the past has been primarily surgical, with von Graefe, the great German surgeon, performing the first closure of a cleft palate in 1816.[9] The early techniques consisted of merely freshening the edges of the cleft and suturing the soft tissue together in the midline. Later on, von Langenbeck and his followers found that something must be done to eliminate the tissue tension accompanying this type of surgery and they made marked lateral re-

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This article is taken from a doctoral dissertation submitted for Ph.D. requirement.

lieving incisions. (Fig. 2.) Numerous modifications were introduced subsequently in an effort to eliminate excessive tension and reopening of clefts, all too often sequelae of surgical soft tissue closure, or staphylorrhaphy. The Krimer Lane technique made use of flaps of mucosa folded over to the midline from the intact palatal processes and sutured together. Granulation tissue filled in the denuded palatal areas. Even then, many operations were unsuccessful.

Coming on the heels of attempts at closure of the cleft palate by soft tissue alone were the mutilating techniques of osteal uranoplasty—or bony closure of the palate. Various methods of binding the separated lateral bony segments together in the midline were suggested. (Fig. 3.) Both extraoral and intraoral appliances were developed to produce a midpalatal bony union, as early in life as possible. (Figs. 4, 5.) Truman Brophy was the foremost proponent of this approach and his powerful influence is widespread in many parts of the country even today.

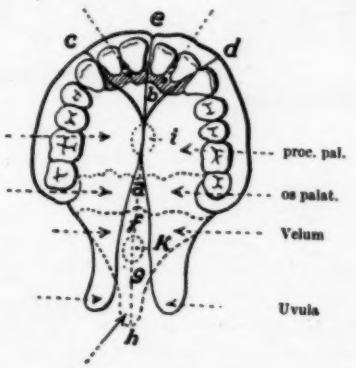

Fig. 1.—Types of palatal clefts: (1) *c-b* and *d-b-a-f-g-h*, complete bilateral cleft palate; (2) *c-b* or *d-b-a-f-g-h*, complete unilateral cleft palate; (3) *c-b-a-f-g-h*, complete median palatal cleft (questionable); (4) *c-b* or *d-b*, anterior or alveolar cleft; (5) *c-b-a* or *c-b-a-f*, incomplete unilateral palatal cleft; (6) *b-a-f-g-h*, incomplete posterior palatal cleft; (7) *g-h*, bifid or cleft uvula; (8) *i* or *k*, palatal perforations, usually of syphilitic origin.

Present-day corrective procedures are basically those developed in the nineteenth century. In most instances they involve surgery, the type and timing of the operation depending on whether the surgeon is a von Langenbeck "soft tissue closure" descendant or a Brophy "steel-clamp-and-silver-wire bony closure" man. There is a basic philosophical conflict between the two major groups. The early pioneers employing staphylorrhaphy for closure of the cleft palate, and contemporary maxillofacial surgeons using variations of the Brown-Dorrance push-back procedures, vomer flap closure, and the radical pharyngeal block technique have stretched and repositioned soft tissue over what they consider a normal bony framework (with the exception of the cleft area) that had failed for some reason to unite in the midline. Brophy adherants are convinced that aberrant embryonal and fetal influences force the lateral halves of the maxilla apart, making the intramaxillary width excessive. For Brophy, it was only

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

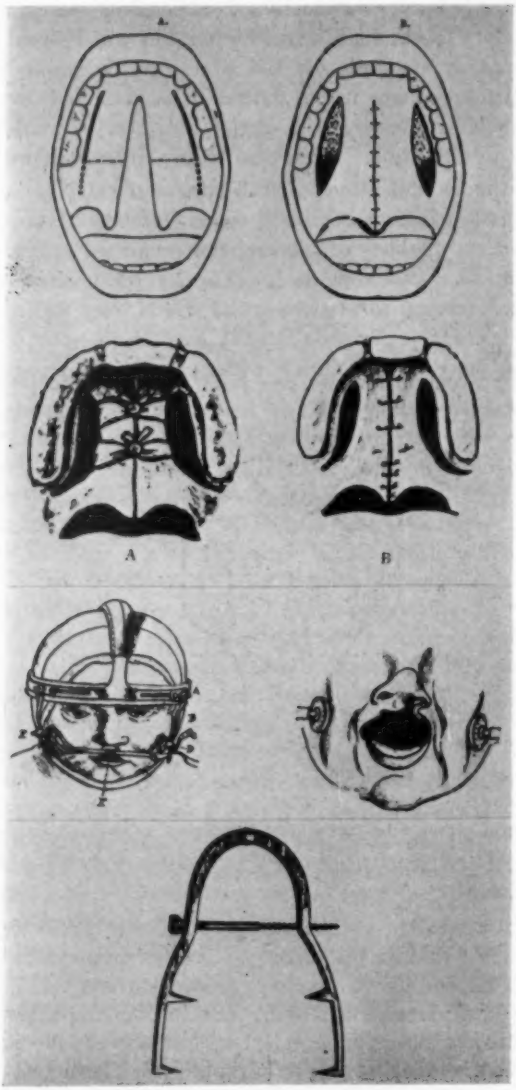

Fig. 2.—The von Langenbeck operation, with marked lateral relieving incisions. (From Dorrance, G. M.: *The Operative Story of Cleft Palate*, W. B. Saunders Company.)

Fig. 3.—The so-called Brophy technique of osteal uranoplasty. The bony segments are forced together and united in the midline to close the cleft. (From Dorrance, G. M.: *The Operative Story of Cleft Palate*, W. B. Saunders Company.)

Fig. 4.—An extraoral appliance to force the lateral bony maxillary segments into contact in order to close the palatal cleft. (From Dorrance, G. M.: *The Operative Story of Cleft Palate*, W. B. Saunders Company.)

Fig. 5.—Intraoral jackscrew type steel clamp for approximating bone in closing cleft palates, devised in 1884, used by Truman Brophy. (From Brophy, T.: *Cleft Lip and Palate*. P. Blakiston's Son & Co., 1923.)

natural that the first step was to restore what he felt was normal segmental relationship. Each school of thought has intense convictions that there is only one correct approach—its own.

Until recently, the surgeon has had to do the job of rehabilitation with little offer of help or counsel from allied fields. The problem has been a difficult one, complicated by the obscure etiology, variations in the nature of the insult, and frequent association with other deformities such as spina bifida, hydrocephalus, and otologic aberrations. Unknown factors of growth and development in this area, questionable prognosis, and psychiatric ramifications have not made the task any easier. Refinements in surgical procedures and advances in asepsis have only served to amplify the shortcomings of cleft palate correction. Surgeons and other students of the problem have slowly recognized that present-day therapy is primarily mechanical in nature. A soft tissue closure of a cleft palate in an infant may seem to be an acceptable result at the time the surgeon is finished, even when the hamular processes have been fractured and the posterior pillars of the nasopharynx involved to reduce the tension caused by the suturing in the midline. But at the end of adolescence a flat fibrous diaphragm may serve as mute testimony of surgical procedures that have been successful only in their steellike grip on futily struggling maxillary growth centers. Before functional failures can be explained, a number of questions must be asked. How does the pattern of growth and development of a cleft palate individual compare with that of a normal one? What is the effect of early and repeated surgical assistance on this pattern? What happens to tissue that has been manipulated and traumatized? Does increased tension of soft tissue stimulate increased proliferation? What is the growth potential of fibrous bands of scar tissue? Can cicatricial bands influence the normal growth and development of the surrounding soft tissue structures and the bony skeleton? How do cleft palate individuals with surgically closed clefts compare with those who have had no surgery?

It is evident that the answers to these questions require a fundamental knowledge of the dynamic processes of craniofacial growth, development, and maturation. The first scientific attempts at appraisal of head development were made by the anthropologists, using dried skulls. The names of Keith, Campion, Hellman, Gregory, and Krogman are familiar to us in this group.[17-21, 23, 24] The heterogeneity of the sampling used by them, unknown history of the individual samples, warpage and shrinkage of dried material, and the need for a cross-sectional approach for the analysis of the material served to detract from the conclusions made on growth. It was the anatomist Todd who said, "A dead child is a defective child," when he challenged the deductions made from young skeletal material.[36] The difficulty of delineating the dynamic nature of the growth processes is illustrated by the anecdote often told of the keeper of the Louvre Museum in Paris who takes his visitors to a special silver trimmed display case housing two skulls, one of an infant, the other of a mature adult. With austere manner reserved for such occasions, he tells his listeners, "the small skull on the left is the skull of Napoleon as a child, the large one on the right is the skull of Napoleon when he died."

Subsequent, more exact techniques have nevertheless verified many anthropologic premises. The early accomplishment of cranial and neural growth, the downward and forward growth of the face, and its emergence from beneath the cranium, the contributions of anteroposterior, vertical and lateral increments in completion of adult cranial and facial form, and growth of the individual bones are basically the same as appraised by the anthropologists. Specifically we learned in our field from Brash and Todd that five-sixths of the total maxillary width is completed by the end of the fourth year of life.[2, 36] Later work by histoanatomists established qualitative and quantitative limits. Sicher has pointed out that maxillary growth in a downward and forward direction is the result of sutural connective tissue proliferation in four major areas (Fig. 6); frontomaxillary, zygomaticomaxillary, zygomaticotemporal and pterygopalatine sutures, supplementing generalized anteroposterior growth by means of the spheno-occipital synchondrosis.[32] Sutural growth is active for almost twenty years. Vital staining techniques with the pig and macaque rhesus monkey (Brash, Schour, and Moore) verify the anthropologic and histologic picture and point to surface apposition of a generalized nature during the first four to five years.[2, 30, 26]

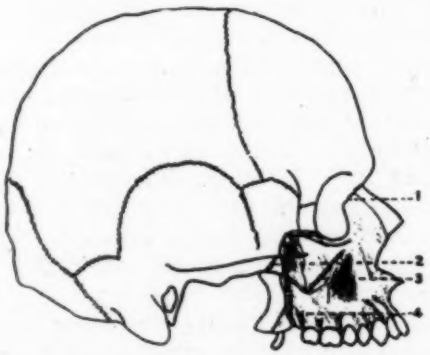

Fig. 6.—Maxillary sutural areas responsible for downward and forward growth, supplementing spheno-occipital synchondrosis. (1) frontomaxillary; (2) zygomaticotemporal; (3) zygomaticomaxillary; (4) pterygopalatine. (From Weinmann, J., and Sicher, H.: *Bones and Bones*, The C. V. Mosby Company.)

Cephalometric roentgenography, introduced by Broadbent in 1931, was a logical step forward for studying cranial and facial growth.[3-5] All factors, except changes within the individual patient, were standardized for the first time. (Fig. 7.) Two x-ray tubes were mounted at 60 inches from the midsagittal and porionic planes for lateral and frontal head plates. The patient was rigidly oriented by means of calibrated ear rods firmly inserted into the external auditory meatus. Broadbent started his study of 5,000 Cleveland school children in 1931 and, following the growth changes within the same individuals, evolved an accurate mensuration of changes in the various components of the face. In 1941, Brodie used the same technique to draw a very complete picture of cranial and facial growth from the third month to the eighth year of life.[6-8] Numerous

investigators have elaborated the contributions of both Broadbent and Brodie in the last ten years.[1, 10, 22, 25, 27, 29, 37] From these various studies of facial growth and development, it is seen that the lateral width of the maxilla is accomplished quite early in life, but that downward and forward growth is not complete until the end of the second decade of life. Any growth disturbance induced by environmental interference would be possible in the sutural sites of proliferation for a number of years, but any appreciable withholding of the palate in width would require interference during the first four years of life.[32] Dorrance apparently sensed this fact clinically when he wrote in 1933, concerning the correct time for surgical intervention in cleft palate, "It is our opinion, as to this point, each case of cleft palate is a law unto itself, the decision as to the proper time to operate being influenced by such factors as the general health of the child, the type and extent of the deformity, and the character of the tissue. We believe that when conditions are favorable, the safest age to operate for cleft palate is about the fifth year. In our experience, operations performed after the fifth year are free from mortality and failures are less frequent."[9] In 1940, the present author wrote, "Cleft palate should be operated upon between 4 and 7 years."[12]

Material for the present study of facial proportions, pattern of growth, severity of deformity and appraisal of therapy was taken from a group of over

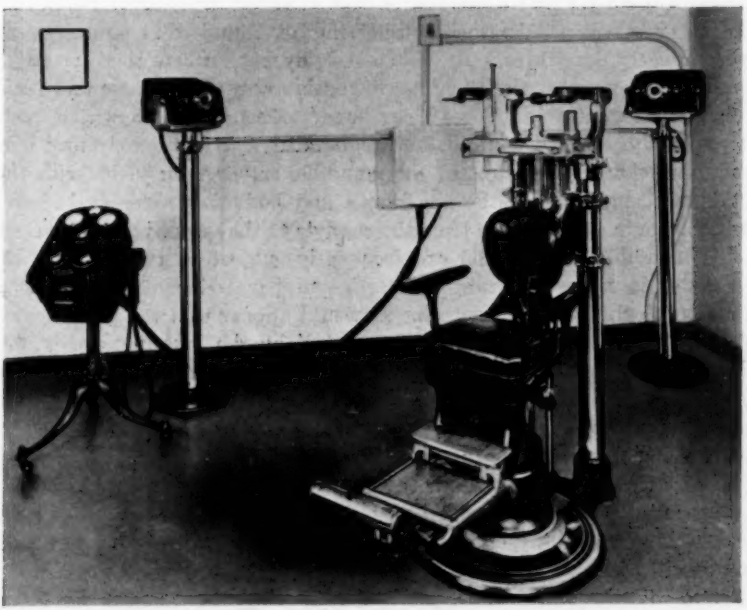

Fig. 7.—The Broadbent Bolton Cephalometer (at Northwestern University). This machine permits an accurate longitudinal roentgenographic appraisal because it rigidly orients the patient's head to a calibrated scale for each picture. The same position can be duplicated a week or a month later by duplicating calibrations and exposure factors. (From the *Quarterly Bulletin*, Northwestern University Medical School.)

TABLE I. FREQUENCY OF TYPES OF CLEFTS

TYPE	MALE	FEMALE	TOTAL	PERCENTAGE
Right unilateral lip-jaw-palate	7	3	10	16.66%
Left unilateral lip-jaw-palate	15	7	22	36.67%
Complete bilateral lip-jaw-palate	10	7	17	28.33%
Split palate without alveolar cleft	4	2	6	10.00%
Alveolar cleft	1		1	1.67%
Split velum and soft palate	1	2	3	5.00%
Unilateral lip, bilateral jaw-palate	1		1	1.67%
Number	39	21	60	
Percentage	65.00%	35.00%		

200 cleft palate patients, ranging in age from 2 weeks to 77 years. An effort was made to include as many cases as possible where no attempt had been made to close the palate surgically. A total of 60 cases make up the basis of the statistical analysis of the roentgenographic phase of the problem. (Table I.)[11-16] Fourteen of these have had no surgery. Criteria of appraisal included upper and lower face height, maxillary height, growth and positioning of upper and lower jaws, position and angulation of the teeth in the facial profile and the intermaxillary clearance.* The intermaxillary clearance is important, for it makes us realize that any study must be in three dimensions. This gives us the vertical component. The lower jaw, at rest and out of active function, is cradled by the facial, masticatory, suprahyoid, and infrahyoid musculature, with the teeth out of occlusion and about 3 to 4 mm. apart in the average person. This is the intermaxillary clearance. Sherrington found that muscles cannot be permanently lengthened or shortened, except by surgical means, and that ordinarily, muscle relationships are considerably more stable and less subject to environmental influences than bone.[31] Sicher has shown in cases of acromegaly with marked mandibular prognathism that the masticatory muscles will actually change the shape of the mandible rather than yield, with the result that the angle formed by the ramus and body is progressively resorbed until it falls on a straight line from the condyle to the symphysis.[32] Conversely, both the mandible and maxilla are frequently subject to growth disturbances which result in malocclusion of the teeth and perversion of the functions of mastication, deglutition, and speech. It would appear that the physiologic rest position of the mandible, which is established by the musculature, is not dependent on bone growth, but on muscular and soft tissue growth, which is seldom abnormal. Studies by Thompson at Northwestern University on normal groups indicate that the physiologic rest position of the mandible is established in infancy and remains constant into senescence.[34, 35] It is thus a valid means of determining the development of both the mandible and maxilla. If both jaws grow normally, then the intermaxillary clearance will be from 3 to 4 mm. If there is either a maxillary or mandibular underdevelopment, the intermaxillary clearance will be larger. (Fig. 8.)

The cleft palate group as a whole showed a marked vertical maxillary deficiency that tended to increase with age. (Figs. 9, 10, 11, 12.) Cephalometric tracings of headplates of a patient whose palate was closed at 3 months of age

*For a complete statistical analysis, see previous articles by the author.[11-16]

Fig. 8.—Comparison of normal intermaxillary clearance of 4 mm. in normal dentition on left with 20 mm. intermaxillary clearance of mutilated cleft palate patient, cast on right.

Fig. 9.

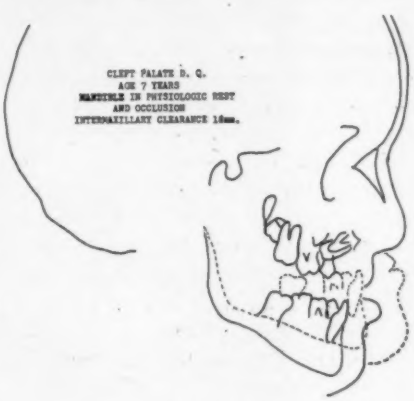

Fig. 10.

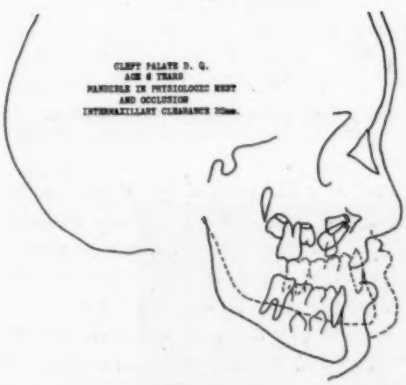

Fig. 11.

Fig. 12.

Fig. 9.—Cleft palate of D. Q., at age 6 years. Mandible in physiologic rest and occlusion. Solid outline shows physiologic rest position of mandible; dotted outline, teeth in occlusion. Note wide range of movement. Intermaxillary clearance 17 mm.

Fig. 10.—Cleft palate of D. Q., aged 7 years. Tracings of mandible in physiologic rest and occlusion. Overclosure of the mandible produces a marked prognathism that accentuates the deformity. Intermaxillary clearance 18 mm.

Fig. 11.—Cleft palate of D. Q., aged 8 years. Mandible in physiologic rest and occlusion. The maxilla remains static in a dynamically growing face. Intermaxillary clearance 20 mm.

Fig. 12.—Cleft palate of D. Q., aged 9 years. Mandible closes 21 mm. from physiologic rest to occlusion. There has been an increase in the intermaxillary clearance of 4 mm. in four years.

show a static maxilla marking time in a face that is growing downward and forward with normal mandibular and soft tissue growth. The intermaxillary clearance, already much too large at 6 years (17 mm.), increases to 21 mm. at 9 years. Lack of maxillary height allows the patient to overclose the mandible, the chinpoint swinging upward and forward into the profile and making the deformity even more acute. Figure 13 shows another example: a cephalometric tracing of a lateral head roentgenogram of a boy whose palate was closed by a Brophy compression-type surgical procedure at 6 months of age. The maxilla is that of a 6-month-old infant, the mandible and masking musculature is that of a 17-year-old boy, which accounts for the wide intermaxillary clearance and marked disharmony in jaw size. The disharmony is manifested not only vertically, as shown by the large intermaxillary clearance, but also laterally and anteroposteriorly. This is quite apparent when comparing those patients who have had early and traumatic surgery with individuals with nonoperated palatal

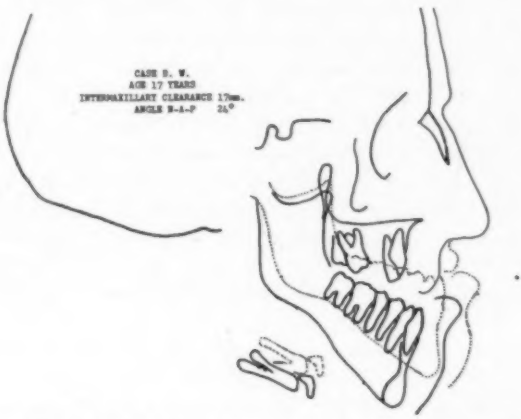

Fig. 13.—Cleft palate of B. W., aged 17 years. Note the markedly concave profile, 17 mm. intermaxillary clearance. Palate was surgically closed at the age of 6 months. (Brophy technique.)

clefts. Figure 14 compares the maxillary cast of a 13-year-old boy whose palate has been closed and maintained that way through a series of fifteen surgical operations, to the cast of a 5-year-old girl with a palatal cleft that is also closed, but by a prosthesis which closes off the oral from the nasal cavity and allows the patient to masticate normally and speak intelligibly. Figure 15 shows the normal relationship of the upper and lower teeth of the 5-year-old girl, as compared to Fig. 16, articulated plaster casts of the 13-year-old boy, seen in Fig. 14. Figure 17 compares the maxillary model of the previous patient with that of a young nonoperated Negro adult. The maxilla of the boy is that of a 3-month-old infant—the size of the palate at the time of the first operation. The palatal tissue is a mass of fibrous cicatricial tissue, taut, flat, and functionless. The maxilla of the nonoperated palate is fully developed and fits harmoniously with the lower jaw during function. This marked growth deficiency in surgically

closed palates shows a direct correlation with the surgical timing and technique: the earlier the operation, the more marked the deficiency; the greater the modelling and displacement of the tissue, the more deficient the maxillary growth. The greater the number of operations, the more scar tissue, and the

Fig. 14.

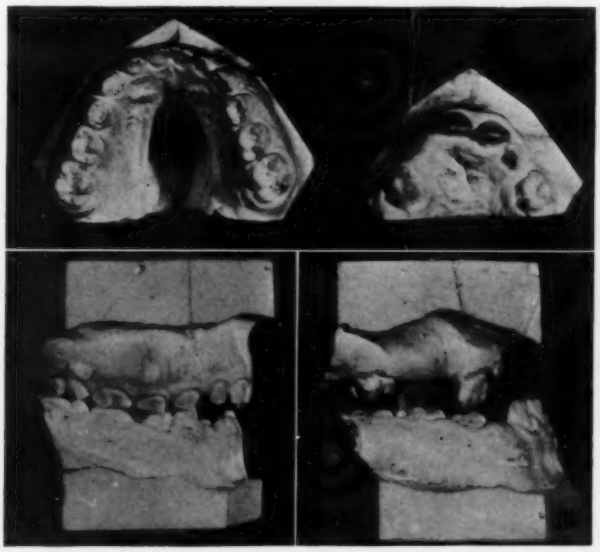

Fig. 15. Fig. 16.

Fig. 14.—Maxillary cast of a 5-year-old girl with an unoperated cleft palate, compared with the maxillary model of a 12-year-old boy who has had fifteen surgical operations to maintain a closed cleft.

Fig. 15.—Articulated dental casts of the 5-year-old girl in Fig. 14. Development is quite normal.

Fig. 16.—Articulated casts of the 12-year-old boy in Fig. 14, showing the maxillary deficiency. Note the lack of teeth because of intramaxillary wiring in first operation at age 3 months, which destroyed the tooth buds.

Fig. 17.—Comparison of cleft palate of L. G., aged 30 years, and cleft palate of R. P., aged 12 years. The cast on the left shows an adult palate where no attempt has been made to close the cleft.

more effective the destruction of the growth centers. That one severe compression closure can create a deformity is shown in Fig. 18, an intraoral view of a 42-year-old male patient whose palate was surgically corrected at an early age. Figure 19 shows a lateral view of his articulated maxillary and mandibular casts. Quite a contrast is provided in the next two illustrations, Figs. 20 and 21, which are intraoral views of nonoperated clefts, closed by plastic prostheses. In both instances, lateral, vertical, and anteroposterior development is within normal limits.

Fig. 18.

Fig. 19.

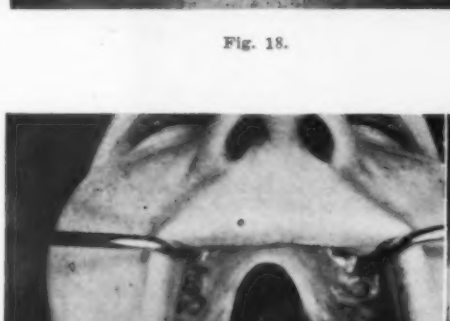

Fig. 20.

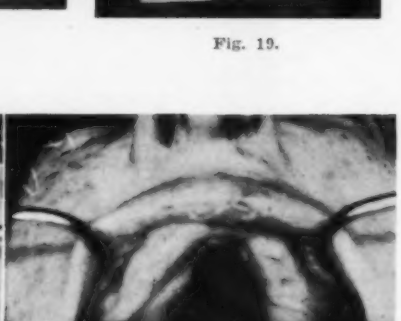

Fig. 21.

Fig. 18.—Cleft palate of J. W. aged 42 years. Intraoral view of micromaxilla and perforation into nasal cavity. Palate was closed at an early age with the assistance of intramaxillary wiring and steel coaptation clamps.

Fig. 19.—Lateral view of articulated plaster casts of J. W., Fig. 18. Note lack of anterior maxillary growth.

Fig. 20.—Intraoral view of nonoperated palatal cleft. Note rampant dental caries and fragmentary teeth. Lack of sufficient means prevented patient from taking care of both cleft and teeth. Teeth, however, can be replaced on a prosthesis that is being made.

Fig. 21.—Intraoral view of edentulous cleft palate, with prosthesis removed to show normal development of tissues contiguous to the cleft.

These case reports seem to indicate clearly that early and traumatic surgical procedures can and do cause gross facial deformities which do not materialize if the cleft palate is left open. But what about those cases where the palate is closed later, with a minimum of tissue manipulation? Many of these patients seem to show a palate whose contour is relatively normal with little or no retardation of middle face growth. Is a palate that apparently is closed successfully as far as configuration is concerned, a *functional* success? Does the repaired palate have a differential rate of growth from the surrounding tissue? It is important to answer these questions, for esthetic success does not justify functional failure. Figure 22, a photograph of a 20-year-old male patient, illustrates a case in point. General facial development is normal, lateral and anterior-posterior dimensions of the palate are within normal limits. Soft tissue closure of the palatal cleft was performed at age 4 years. An analysis of muscle relations during function yields a different story. Both anterior and posterior pharyngeal pillars are taut. The musculus uvuli is functionless.

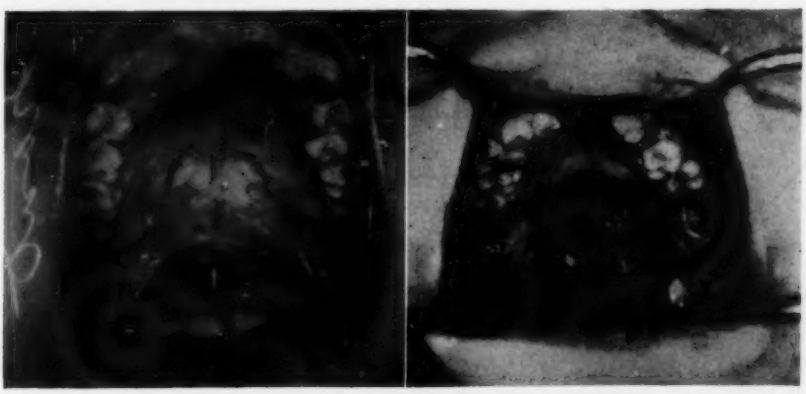

Fig. 22. Fig. 23.

Fig. 22.—Cleft palate of R. B., aged 20 years. Cleft closed at age 4 years with relatively slight malformation. Note, however, taut, curtainlike anterior and posterior pharyngeal arches which exert considerable downward pull on the soft palate.

Fig. 23.—Another repaired cleft palate with little growth disturbance. Velopharyngeal valving is impossible, however, as a result of the foreshortened, scarified, functionless soft palate.

The levator palati muscles show no contraction during any phase of mastication and deglutition. The tensor palati muscles which normally elevate the soft palate to the constrictor ring formed by the superior fibers of the superior constrictor muscle (Passavant's ridge) contract, but cannot overcome the downward pull of both the pharyngopalatinus and glossopalatinus muscles. The patient complains of increasing difficulty in swallowing and an increased nasality of tone, especially marked during the past five to six years. At 4 years of age the closure of the cleft was a success. At 14 years, the patient noticed difficulty of function. At 20 years, the structure is completely inadequate for eating, swallowing, and speech. What seems to happen is that the repaired soft tissue

Fig. 24.—Plaster casts demonstrating how a prosthesis can restore the lost vertical dimension of a mutilated cleft palate. Without the prosthesis, the lower jaw closes upward and forward into an acute prognathism which completely enclosed the micromaxilla.

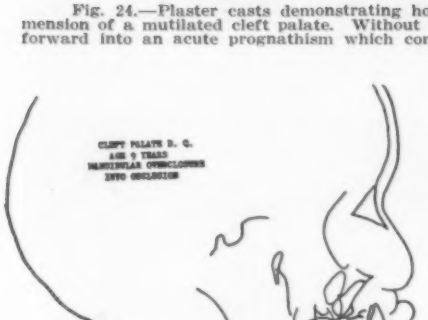

Fig. 25.

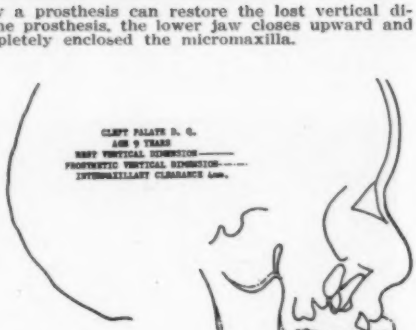

Fig. 26.

Fig. 25.—Cephalometric tracing cleft palate in D. Q., aged 9 years, shows teeth forced into occlusion by mandibular overclosure.

Fig. 26.—Cleft palate of D. Q., aged 9 years. Same patient as in Fig. 25. Solid outline shows mandible in physiologic rest position. Broken outline is of mandible with prosthesis inserted to restore maxillary vertical deficiency and to prevent overclosure seen in Fig. 25.

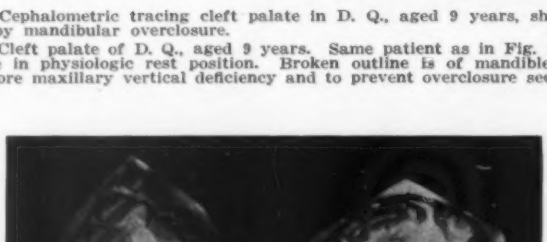

Fig. 27.—Cast (left) of cleft palate patient whose palate repair has finally sloughed away after repeated attempts to maintain closure. Cast (right) taken during orthodontic treatment to illustrate the results of actual shifting of the lateral segments of the maxilla, in conjunction with tooth movement.

palatal mass grows more slowly than the surrounding tissue, anchored as it is by scar tissue bands to the rudimentary bony palatal processes. The posterior wall of the nasopharynx descends downward and backward during growth, but the soft palate doesn't go with it. Despite the fact that the superior constrictor muscle shows considerable compensatory contraction, its increased activity cannot make up for the ever-widening gap. The tensor palati muscle gradually loses its function of elevating the soft palate and serves only as a ventilator for the pharyngotympanic tube. Figure 23 again illustrates the functional inadequacy of a surgically repaired palate.

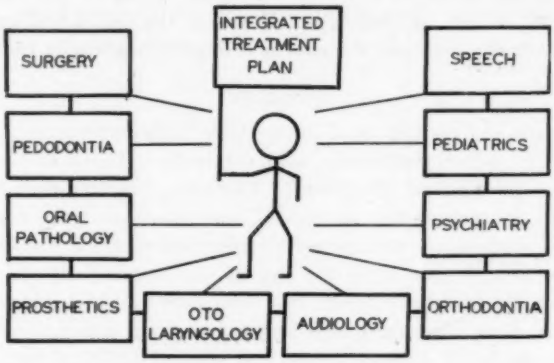

Fig. 28.—The essential elements for complete cleft palate rehabilitation.

What then should be done for these patients? The first goal should be to maintain whatever normal structures there are already.[33] Second, missing parts and normal structural relationships should be restored. If this can be done by using the patient's own tissues, so much the better, but in most cases this is impossible and resort must be had to prosthetic restoration. Figure 24 demonstrates one method of eliminating the vertical deficiency that results from interference with growth centers. A denture was constructed over the diminutive maxillary arch to restore an occlusal plane in harmony with normal mandibular development and position. Figures 25 and 26 are cephalometric tracings, again demonstrating the use of a prosthesis to restore normal face height and function, eliminating perversions of the temporomandibular articulation. Figure 27 shows the plaster maxillary casts of a patient whose palatal repair had sloughed away after repeated attempts to maintain closure. The jumbled array of teeth was corrected, as shown in the progress cast on the right, and then a prosthesis placed with an attached speech appliance for subsequent speech therapy.

Treatment of the cleft palate individual should not be left to any single specialist, whether he be a surgeon, pediatrician, prosthodontist, orthodontist, or speech therapist.[33] All must coordinate their services to achieve the best over-all result, rather than concentrate only on their particular phase of the problem, as has been done only too often in the past. (Fig. 28.) The Cleft

Lip and Palate Institute of Northwestern University and Children's Memorial Hospital in Chicago is a step in the right direction. When a patient enters the Institute, each member of the staff gets those records which he considers essential for a diagnosis. The records include complete case histories, cephalometric roentgenograms, dental radiographs, audiometric tests, aptitude and intelligence appraisals, surgical, pediatric, speech, dental and orthodontic consultations, and psychiatric review if necessary. These records are then correlated by the director, Dr. John R. Thompson, and the entire staff goes over the case in round table conference and together decides on treatment. The patient or his parents may question any member of the panel on any aspect of treatment. Therapy is then instituted, but if any of the individual members of the staff seek further consultation, the case is brought up again in panel conference.

SUMMARY

Cleft palate individuals as a group show deficient patterns of maxillary growth, laterally, anteroposteriorly, and vertically. Early and traumatic surgery results in the greatest deformity. There is a positive correlation between the number of operations, the amount of scar tissue, and the degree of insult. To minimize interference with growth centers, it seems advisable to postpone surgical correction at least until the end of the fourth year of life, when five-sixths of the total maxillary width has been accomplished. However, it must be remembered that downward and forward growth, which depends primarily on the spheno-occipital synchondrosis and sutural activity continues until 20 years of age. It appears that the surgically repaired palate grows more slowly than the surrounding soft tissue. This results in increasing functional difficulty and ultimate structural inadequacy. Patients whose palatal clefts have not been surgically manipulated show a pattern of maxillary growth that is essentially normal. Closure of nonoperated clefts by prostheses seems quite successful, if judged by the general intelligibility of speech and ease of mastication and deglutition. Rehabilitation requires the coordination in one organization of all the skills and knowledge peculiar to the cleft palate problem. Only by grouping services and correlating information and ideas can each man render the fullest value of his particular field.

REFERENCES

1. Baldridge, J. P.: A Study of the Relation of the Maxillary First Permanent Molar to the Face in Class I and Class II Malocclusions, Angle Orthodont. **11**: 105, 1941.
2. Brash, J. C.: The Genesis and Growth of Deformed Jaws and Palates, The Dental Board of the United Kingdom, London, 1924, pp. 67-107. (Pamphlet.)
3. Broadbent, B. H.: A New Technique and Its Application to Orthodontia, Angle Orthodont. **1**: 45, 1931.
4. Broadbent, B. H.: The Face of the Normal Child, Angle Orthodont. **7**: 185, 1937.
5. Broadbent, B. H.: Measurement of Dento-Facial Changes in Relation to the Cranium, in: Practical Orthodontia, Dewey, M., and Anderson, G. M., ed. 5, St. Louis, 1935, The C. V. Mosby Company, pp. 184-204.
6. Brodie, A. G.: The Growth Pattern of the Human Head From the Third Month to the Eighth Year of Life, Ph.D. Thesis, Department of Anatomy, University of Illinois, 1940.
7. Brodie, A. G.: The Growth Patterns of the Human Head, Am. J. Anat. **68**: 209, 1941.
8. Brodie, A. G.: The Growth of the Jaws and the Eruption of Teeth, Angle Orthodont. **12**: 109-123, 1942.

9. Dorrance, G. M.: The Operative Story of Cleft Palate, Philadelphia, 1933, W. B. Saunders Company.
10. Downs, W.: Variations in Facial Relations; Their Significance in Treatment and Prognosis, Am. J. Orthodontics **34**: 10, 812-840, 1948.
11. Gilley, F. P.: Dento-Facial Morphology in Cleft Palate, Master's Thesis, Northwestern University, Department of Orthodontics, 1947.
12. Graber, T. M.: Cleft Palate and Harelip, Washington Univ. D. J. **6**: 76-83, 1940.
13. Graber, T. M.: Craniofacial Morphology in Cleft Palate and Cleft Lip Deformities, Surg., Gynec. & Obst. **88**: 359-369, 1949.
14. Graber, T. M.: The Growth and Developmental Factors in Cleft Palate Patients, Angle Orthodont. **19**: 68-76, 1949.
15. Graber, T. M., and Merrifield, F. W.: An Appraisal of the Developmental Deformities in Cleft Palate and Cleft Lip Individuals, Quart. Bull., Northwestern Univ. M. School **23**: 153, 1949.
16. Graber, T. M.: Orthodontics for the Cleft Lip and Cleft Palate Patient, Fortnightly Rev. **18**: 9-13, 1949.
17. Gregory, W. K.: Our Face From Fish to Man, New York, 1929, G. Putnam's Sons.
18. Hellman, M.: Changes in the Human Face Brought About by Development, Int. J. Orthodontia **13**: 475-516, 1927.
19. Hellman, M.: An Introduction to Growth of the Face From Infancy to Adulthood, Int. J. Orthodontia **18**: 777-98, 1932.
20. Hellman, M.: The Face in Its Developmental Career, Dental Cosmos **77**: 685-700, 777-787, 1935.
21. Hellman, M.: Some Facial Features and Their Orthodontic Implications, Am. J. Orthodont. & Oral Surg. **25**: 927-51, 1939.
22. Herzberg, B. L., and Holic, R.: An Anthropometric Study of the Face Height, Am. J. Orthodont. & Oral Surg. **29**: 90-100, 1943.
23. Keith, Sir A., and Campion, G.: A Contribution to the Mechanism of Growth of the Human Face, D. Record **8**: 607-33, 1922.
24. Krogman, W. M.: Facing Facts About Face Growth, Am. J. Orthodont. & Oral Surg. **25**: 724-31, 1939.
25. Mayne, W. R.: A Study of the Skeletal Pattern of the Human Face, Master's Thesis, Department of Orthodontics, Northwestern University, 1946.
26. Moore, A. W.: Head Growth of the Macaque Monkey, Am. J. Orthodontics **35**: 654, 1949.
27. Ortiz, M. H., and Brodie, A. G.: On the Growth of the Human Head From Birth to the Third Month of Life, Anat. Rec. **103**: 311-34, 1949.
28. Peyton, W. T:. Dimensions and Growth of the Palate, Arch. Surg. **22**: 704-737, 1931.
29. Riedel, R. A.: A Cephalometric Analysis of Craniometric and Anthropologic Measurepoints, Master's Thesis, Department of Orthodontics, Northwestern University, 1948.
30. Schour, I. M.: Post-Natal Cranio-Facial and Skeletal Development as Demonstrated by Vital Injections of Alizerine Red S, Anat. Rec. **76**: 94, 1940.
31. Sherrington, C. S.: Note on Certain Reflex Actions Connected With the Mouth, Brit. D. J. **31**: 16, 1910.
32. Sicher, H.: Oral Anatomy, St. Louis, 1949, The C. V. Mosby Company.
33. Slaughter, W. B., and Brodie, A. G.: Facial Clefts and Their Surgical Management in View of Recent Research, Plast. & Reconst. Surg. **4**: 311-332, 1949.
34. Thompson, J. R.: The Rest Position of the Mandible and Its Significance to Dental Science, J. A. D. A. **33**: 180, 1946.
35. Thompson, J. R.: The Rest Position of the Mandible and Its Application to Analysis and Correction of Malocclusion, Angle Orthodont. **19**: 162-187, 1949.
36. Todd, T. W.: The Orthodontic Value of Research and Observations in Developmental Growth of the Face, Angle Orthodont. **1**: 67, 1931.
37. Toothaker, J. C.: A Study of the Angle of Axial Inclination Between the Teeth and Their Bony Bases, Master's Thesis, Department of Orthodontics, Northwestern University, 1946.
38. Voorhees, I. W.: Causes of Surgical Failures in Cleft Palate Operations, Am. J. Surg. **11**: 588-595, 1938.

Psychologic Aspects of Pediatrics

CHILDHOOD SCHIZOPHRENIA

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SCHIZOPHRENIA in children has been defined by Bradley[1] as a severe mental illness in which the distinguishing characteristic is a withdrawal of interest in the environment. There is a diminution of appropriate emotional response to real situations, a loss of interest in the world of reality, and, at the same time, preoccupation with an inner imaginary world. The term "schizoid" designates subjects in whom the personality defect is similar to that seen in schizophrenia but is not as extreme.

INCIDENCE

Schizophrenia in adults is one of the most frequent of human ills. In the United States approximately 150,000 individuals are institutionalized annually for this ailment. In addition many schizophrenics are outside of institutions. They are said to make up a considerable proportion of the incompetents, hoboes, prostitutes, and criminals in society.

Schizophrenia is being recognized with increasing frequency in children. Despert[2] reported on 29 cases from the New York State Psychiatric Institute between 1930 and 1937. Bender in 1947[3] based her analysis on 100 children seen on the Children's Ward of the Psychiatric Division of Bellevue Hospital over a ten-year period. Bradley[1] reported 14 cases.

ETIOLOGY

Psychotic antecedents are frequently found in the family histories. About 10 per cent of all schizophrenics are the children of parents with the disease.

An unhappy environment which leads a child to substitute an inner world of fantasy for the outer world may precipitate symptoms in a susceptible child.[2] According to Despert[2] the mothers of children with schizophrenia present definite personality characteristics. They are aggressive, overanxious, oversolicitious, and they often completely reject the child. Peck, Rabinowitz, and Cramer[4] regard these as reactions to the schizophrenic child and not as etiologically related. They found that the parents were unusually difficult to manage. Children were brought unwillingly, treatment was often terminated hardly before it had been begun, and information about the child and family interrelationships was withheld. The authors attribute this behavior to the peculiar nature of the illness. The child with schizophrenia clings to the mother, continually seeking contact with her, yet his lack of emotional response makes her feel rejected and confused.

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The parental reactions toward the child with schizophrenia are: confusion owing to inability to understand the child's behavior, an intense sense of guilt, anxiety, and, in addition, hostility. The hostility is generated by the child's constant demands for affection and attention, his own overt hostility toward the parents, the disrupting influence of his behavior on the relations within the home, his disturbances in the neighborhood and among friends.

Age.—Bender[3] mentions three critical periods for the onset of schizophrenia in children, the first two years of life, between 3 and 4½ years of age, and between 10 and 11½ years.

SYMPTOMATOLOGY

According to Bradley[1] the most frequent symptoms of schizophrenia in children are (1) seclusiveness and (2) irritability when seclusiveness is disturbed. These two characteristics generally appear early in the disease and were observed in all of his fourteen patients.

Other manifestations are (3) daydreaming, or preoccupation with thoughts and fantasies definitely in excess of what is usually seen in children of similar age and developmental status; (4) bizarre behavior which consists of incongruous actions and activities such as repetitive, purposeless motions, unintelligible language, and irrelevant expression of emotion; (5) diminution of interests or failure to be attracted by objects and activities which one usually anticipates in children of similar age and intelligence; (6) regressive personal interests or the voluntary selection of and participation in amusements and occupations which customarily intrigue children of younger age levels; (7) sensitivity to comment and criticism, i.e., excessive emotional response to such personally directed opinions of others as praise, blame, and so on; and (8) physical inactivity, i.e., conspicuously less gross motility than is commonly seen in other children of the same age and developmental status. (Often the reverse is true and motility is excessive.)

Bender,[3] who has observed more than 100 preadolescent children suffering from schizophrenia, regards the condition as an encephalopathy. The afflicted child reveals abnormalities in behavior at every level and in every area of integration or patterning within the central nervous system. The vasovegetative, motor, perceptual, intellectual, emotional, and social spheres are all involved. The severity and nature of the involvement of each of these areas vary from patient to patient and in the same patient from time to time depending on his own personality make-up, his developmental status, and his life experiences.

A prominent feature of the clinical picture is anxiety. It represents the individual's reaction to the disrupting effects of the disease. How he manifests his anxiety depends on his developmental status and his innate capacities. In some patients anxiety is the dominant feature of the condition. Common behavior among afflicted children on first entering the office is to open doors and peer behind them anxiously.

Vasovegetative Functioning.—Among the disturbances in this sphere Bender mentions the following: (1) excessive lability. Flushing and perspiring, or pallor with blue, cold extremities; (2) unpredictable reaction to illness. Excessive reaction to minor illnesses, mild reaction to severe illness; (3) loss of rhythmic patterning of sleeping, eating, bowel, and urinary activities; (4) discrepancies in growth, the children being too large or too small, too fat or too thin; (5) accelerated or delayed puberty.

Motor Functioning.—Characteristic disturbances in motor functioning are seen in the child with schizophrenia. Motor development may be irregular and motor awkwardness is common. New motor patterns are approached with anxiety and old motor habits may be lost with the onset of the illness. There is great dependence on the mother in the formation of new motor habits. The child may be excessively timid about walking alone, climbing stairs, stepping over or off small objects, using swings and tricycles, or even remaining alone in the carriage or high chair.

Early or primitive reflex activities are often retained beyond the developmental stage to which they belong. Among these may be mentioned the postural reflex responses which are characteristic, but not pathognomonic of this condition. These are elicited in the following manner: The child stands with the arms extended in front of him and his eyes are closed. The examiner then rotates the child's head to one side. The primitive response to this test is to turn the body so that it is in line with the head. So long as the examiner continues to turn the head the child continues to turn on his longitudinal axis. Such a response is normal for children from the time they are able to cooperate with the test until about 6 years of age. Thereafter the normal child will accept the turning of the head without rotating the body. After an initial displacement of the arms, he will correct the displacement.

The child with schizophrenia, on the other hand, "responds to this test with a graceful fluid whirling which he quickly accepts as a new pattern of activity, if he has not already discovered it himself, and will carry it on spontaneously. Sometimes the examiner need only put his finger on the top of the head which suggests a pivot." To the child with schizophrenia the test stimulus is pleasing and conforms with his own impulses. Rotating and whirling play make up a large part of his activity.

Bender describes two other related phenomena, both of which are manifestations of the bodily dependence of the child with schizophrenia. They are elicited by simple physical contact, the patient seeking to use the body or the motility of the examiner as a substitute for his own. The child will lean so completely against the adult that he will fall to the ground if support is abruptly withdrawn or he will sink into the lap or arms of the adult completely and passively as though "to melt his own body into that of the other and thereby identify himself with the other's more secure center of gravity." In the same way he clings to the adult at every opportunity.

The second phenomenon is an unusual cohesiveness of the body surface with that of the examiner. When the palm of the examiner is placed in that

of the patient, the patient can be pushed about at will maintaining continuous contact only by the cohesiveness of the skin surfaces. In eliciting this phenomenon it is often necessary to overcome an initial resistance on the part of the patient.

Preoccupation with motor play is not infrequently observed. The child often carries on endless rhythmic and graceful dancing behavior interrupted by abrupt, aimless, darting movements. Other disturbances of motor control are grimacing, oral mannerisms, often accompanied by oral noises, and change in the voice which may be high-pitched, metallic in quality, sing-song, etc.

Perception.—The child with schizophrenia sees the world in a strange and peculiar way. It is to him a menacing and ever changing force without fixity or stability. In his efforts to grapple with problems he sets up unusual relationships and he symbolizes. He fails to distinguish between the important and the unimportant.

Intellectual Functioning.—Bender describes the thought processes of the child with schizophrenia as "vortical, gyrating, circling about a nuclear point of gravity which cannot be fixated." Excessive concern is often shown with philosophic problems of existence such as life, death, and life after death, and there is unusual insight into abstract phenomena. In addition the reaction to threatening symbols may be excessive.

Since verbal expression can hardly be expected to keep pace with the rapidity of ideation what the patient expresses in language sometimes sounds fragmented, dissociated, and bizarre.

Schizophrenia, occurring during the early years of life, may manifest itself principally by developmental retardation, especially in speech. Mutism may be the initial symptom which brings the patient to the physician. When speech is already present there may be regression and, with it, the use of simpler language forms, omission of connecting words, and fragmentary speech. The afflicted child uses speech to voice his anxieties and uncertainties and as an expression of his motor drives. Common deviations in speech are the use of occasional explosive expletives, aggressive or obscene in nature; repetitive or perseverative speech; experimental use of words with the formation of new words; using the third person pronoun for himself. Children normally refer to themselves by the third person until about 3 years of age but thereafter the persistence of this immature form of behavior is an indication of the child's pathologic relation to the outside world in that he is unable to distinguish the "I" and "not I."

Children who develop schizophrenia later in childhood often show precocious facility in the field of language.

Emotional Functioning.—Fear states, panic, bewilderment, and apathy are reactions commonly seen in the child with schizophrenia. Anxiety is a prominent manifestation at all stages. An inability to tie up emotionally with people in his close environment is considered a pathognomonic sign by Despert.[5] On the other hand, the child may over-identify with persons about him.

Social Relationships.—Children with schizophrenia are, on the whole, attractive and intriguing. The older ones appear gifted because of their interest in art and philosophic problems and their facility in symbolic expression. For these reasons they are generally well liked and there is a tendency for adults to over-identify with them. Their problems in the home are often exaggerated by the presence there of other individuals with schizophrenia.

PSYCHOLOGIC TESTING

Psychologic testing usually yields results which are of diagnostic value (des Lauriers and Halpern[6]).

The General Mental Level (I. Q.).—In the majority of cases results of I. Q. testing are not representative of the subject's true mental level. Though some patients differ little in performance from average children others show considerable unevenness in functioning. No one pattern is significant or diagnostic of childhood schizophrenia.

A striking characteristic of the schizophrenic test performance is an unexpected and unpredictable break which occurs irregularly in the sequence of his successes and which appears to be unrelated to the difficulty of the task. In testing the average child there is a fairly even progression of successes with failures increasing as the tasks become more difficult. In the child with schizophrenia the failures and successes take place in jumbled fashion and consequently the final score seldom has true predictive value. The poor responses may be the result of sudden preoccupation with some small irrelevant detail with neglect of the main issue; or they may be the manifestation of inner, uncontrollable pressures, with atypical associations and formulations. Consequently the response is not only incorrect, it often appears illogical. Even correct responses may be arrived at by unusual lines of reasoning.

In general, disturbances in thinking may be evident in any test item and are not confined to certain specific functions. The child's reaction is determined, in large measure, by what catches his awareness at the moment and by what kind of association this particular stimulus arouses.

Goodenough Draw-A-Man-Test.—Des Lauriers and Halpern found that the results with this test are in no way a measure of the intelligence of the child with schizophrenia. The test is, however, of considerable value as re-

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(Legend continued from opposite page.)

The uncertainty and anxiety revealed in the hesitant, faint, broken body lines seems related to a concept of the self as unpleasant, unattractive, and inadequate. There is no attempt to embellish the figure with any details. Actually it consists of just the barest oulines, with the absence of hair particularly pointing to feelings of insufficiency. This lack of decoration makes all the more significant the one little adornment the patient produced, namely the row of buttons down the front of the coat. These are generally considered as symbolic of umbilical attachment and point to exaggerated dependency.

The disturbances this boy experiences are probably producing aggressive behavior. The clawlike fingers and the squared body are generally found where aggressive behavior prevails. However, the relative shortness of the arms and their displacement toward the neck and head suggest that he is not secure or very successful in his aggression.

In summary, this is a very anxious boy with strong feelings of inadequacy and a sense of disorganization. His efforts at handling his disturbances and compensating for his shortcomings and deviations are not very successful or reassuring to him. The drawing coincided with the findings on other tests and suggested that this boy was suffering from schizophrenia. Diagnosis was confirmed by psychiatric consultation.

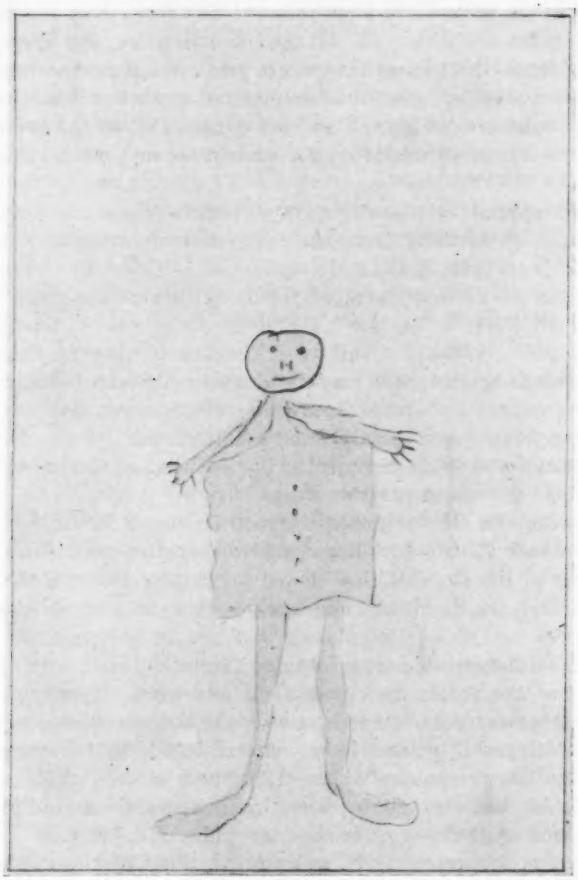

Fig. 1.—Drawing of a 9-year-old boy with schizophrenia. The principal complaints were: "Slow in school, doesn't get along with children, is contrary, stubborn and unresponsive. Average intelligence." Interpretation of the drawing is by Mrs. Florence Halpern, Instructor in Medical Psychology, New York University, College of Medicine.

The striking features are the contrast between the definiteness with which the lines of the head are drawn and the uncertainty and vagueness of the rest of the figure, the displacement of the arms, the distorted body proportions, and the placement of the figure at the very bottom of the page.

From the contrast between head and body lines it would seem as though this boy were confused about the nature and structure of his own body and the relation between it and the various members attached to it. Actually, neither the head, the arms, or the legs are firmly connected to the torso. A lack of a strong, reassuring sense of integration is reflected here. There is a distinct separation between the head which, as the seat of the intellect, represents control and the body which houses the more primitive impulses. The general disconnectedness suggests not only a definite absence of control but also a feeling of inefficiency and ineffectualness in meeting various life experiences.

The patient attempts to compensate for his uncertainty and confusion by giving himself a very solid base (large feet) and attempts to give some definiteness to his concepts of himself by squaring off the body. His need for stability and support are reinforced by the fact that he does not center the figure as more secure children do, but must place it at the bottom of the page. Centering it would probably leave this boy with a feeling of hanging in space, something his uncertainties could not tolerate.

(Continued on opposite page.)

vealing some of the child's inner preoccupations. Sometimes the figures which the children draw are distorted, flat and meaningless, and empty of detail. On the other hand the figures may show great detail in the head, feet, and hands. The test reveals, by what is emphasized and what is subordinated, the way the child conceives of himself and his relationship to the outside world.

Drawings.—The drawings often show confusion and mental disorganization such as:

Disturbed spatial relationships, for example the arms coming off the head, the hands protruding from the body without arms, a series of hands coming out from all parts of the body, and so on.

Elongations of various parts of the body, protrusions, deliberate omissions.

Overemphasis on the extremities. The hands, fingers, fingertips, feet, toes, facial features, and hair may be drawn with careful but bizarre detail while the remainder of the figure may be more or less neglected.

A tendency to project a spiral motion into the lines.

Transparencies showing introjected bodies; that is, the incorporation into the body of objects from the outside world.

The drawing of a child with schizophrenia is shown in Fig. 1.

*The Rorschach Test.**—The Rorschach test may be helpful in revealing the particular way of life the child has chosen for getting along in the world. Des Lauriers and Halpern divide the responses of children with schizophrenia into two groups:

1. The records resemble those obtained from children with organic brain disorder. They are short, show poor form and even bizarre responses, have a tendency to perseveration (that is, giving the same responses to many of the plates), lack adaptability, and have general intellectual and emotional impoverishment. The responses differ from those of the child with organic brain disease in that the child with schizophrenia seems indifferent to the whole procedure while the organic child struggles with his task.

2. The responses resemble in many ways those of the neurotic child in showing doubt and uncertainties. However, the records of the child with schizophrenia show sudden and unexpected changes in odd ways and unusual places. In addition there may be sudden refusal of one of the Rorschach plates, often one which is generally considered easy.

Throughout the examination the child reveals anxiety in every conceivable way—vague, general anxiety; expression of fear of attack from the outside world; a strong need to cling to something postive, and so on.

Thematic Appreciation Test.†—The child with schizophrenia often builds up dramatic stories which may have no relation whatever to the picture which is presented. The tales may be fantastic and concern such abstract problems as life, death, God, and the devil. In addition he tends to interpret the pictures as referring to himself.

*The test consists of ten symmetrical, variously colored and differently shaped ink-blots, which are presented to the patient, one at a time, for description and comment.

†The test material consists of a series of pictures about which the subject is asked to tell a story.

DIFFERENTIAL DIAGNOSIS

Schizophrenia must be distinguished from simple mental retardation, delayed development in beginning to talk, organic disease of the brain, and a behavior disorder based on disturbances in interpersonal relationships. The diagnosis of schizophrenia should be suspected in every severely disturbed child. During the early years (3 to 5 years) disturbances in speech, such as mutism, regressions, neologisms, and fragmentary speech, are prominent manifestations. Other suggestive symptoms are seclusiveness, unusual preoccupation with trifles, withdrawal of interest, oral mannerisms (biting, sucking, grimacing), changes in motility (over- or underactivity, motor habits) and excessive anxiety which often evidences itself as clinging or marked negativism.

In schizophrenia, as distinguished from simple mental retardation, development proceeds normally at first and then either slows down or deteriorates. Moreover, the disturbance in mental functioning of the schizophrenic is likely to be irregular and to affect certain faculties, for example speech, more than others. When the disease starts during the first two or three years of life, the mental deterioration may not be readily apparent. In such instances the diagnosis must be made on the presence of other manifestations of the disease.

In organic disease of the brain the diagnosis is made on the following symptoms: a history of a traumatic episode such as difficult birth, postnatal anoxia, early attack of whooping cough, encephalitis and so on; slow but progressive development; a behavior disorder characterized by overactivity, restlessness, impulsiveness, distractibility, and poor concentration; signs of neurologic disease which may be overt and readily demonstrable or slight and elicited only by careful postural examination; perceptual and conceptual difficulties which may be elicited by paper-pencil tests and the marble-board test of Werner and Strauss.[7] Anxiety is usually present but is not as marked as in schizophrenia.

Severe behavior disorders, accompanied by excessive anxiety, are sometimes distinguished with difficulty from schizophrenia. In such instances the children should be referred to an institution where they can receive prolonged psychiatric observation.

Electroencephalographic changes are frequent in children with schizophrenia but the abnormalities are in no way characteristic.

Early Infantile Autism.—A condition closely related to schizophrenia has been designated by Kanner[8] as early infantile autism. The children appear unable to make normal contact with their environment or to relate themselves in the ordinary way to people and situations from the beginning of life. From early infancy they appear self-sufficient and completely uninterested in the people about them or in what they were doing. On the other hand they use objects well, have great manual dexterity, and surprising memory. It is characteristic that they like familiar objects and situations, repeatedly building the same block forms and becoming agitated by any change in physical surroundings. Most are originally considered feeble-minded.

These children are aware of the presence of others but they appear unaffected by them. They do not listen or respond and consequently many have been considered deaf. Speech is delayed but eventually the majority of those studied (thirteen out of twenty) acquired the ability to speak. Naming seems to present no difficulty and even long and unusual words may be retained with remarkable facility. An excellent rote memory is characteristic, and poetry, songs, list of presidents, and the like may be repeated.

When sentences are finally formed they are, for a long time, parrotlike repetitions of word combinations previously heard. "Yes" is a concept that is difficult for them to acquire. They tend to use words literally and inflexibly. But even after they begin to talk, speech still lacks relationship to the environment. It seems to be learned as a parrot does without understanding. They lack the ability to differentiate "you" and "I," they do not say "yes" and "no" but repeat the question asked or the answer given. Speech is not free and there is no spontaneous conversation. Some slight improvement takes place after the age of 6 years, the child perhaps being able to use the first instead of the third person in referring to himself. Vocabulary is good, but conversation is never initiated.

People seem to them to be no more than objects. When annoyed by someone the child gets angry, not at the person but at the part annoying him, the hand which took away the toy, and so on. After the toy is returned further interest ceases. The child is shut-in and self-sufficient.

Kanner calls this type of behavior extreme autistic aloneness (sufficient unto themselves). In his series it was four times as common in boys as in girls. Most of the children came from homes where the parents, grandparents, etc., were professional people. They were highly intelligent and successful and many were prominent. Obsessiveness was prominent in the family backgrounds. The parents were not warmhearted; rather they were preoccupied with abstractions, science, literature, and so on, and not with people. Even marriage was cold and formal.

Kanner offers no further explanation as the etiology of this condition. Can it be that these children lack love, affection, and tenderness and so develop a preference for aloneness? Against this is the fact that the lack of interest in people was present very early in life. They did not show any anticipatory posture preparatory to being picked up as do normal children by the fourth month. On the other hand, Kanner asks, can this lack of interest in people be inherited from the parents in an exaggerated form? He suggests no treatment.

The children cannot be properly tested with the Binet or other intelligence tests but they succeed easily with the form board. They have excellent memories and the speaking children have good vocabularies. They are unquestionably endowed with good cognitive potentialities. Mostly they are serious-minded and tense and, when not bothered by people, they appear placid and happy.

Heller's Dementia Infantilis is characterized by mental deterioration following a period of normal mental development. The disease begins at 1½ to

4 years of age and involves all aspects of mental functioning. Physical and motor development proceed normally or are only moderately retarded. Biopsy of the cerebral cortex reveals shrinking, vacuolation and coarse clumping of the Nissl substance.

It is likely that most instances of Heller's disease represent a severe form of childhood schizophrenia.[9] Some may be due to encephalitis. Histologic changes, similar to those seen in Heller's disease, have also been observed in patients with schizophrenia.

PROGNOSIS

According to Bradley[10] and Despert[5] the prognosis in schizophrenia of childhood is uniformly bad. This has not been the experience on the Children's Psychiatric Division of Bellevue Hospital, possibly owing to different diagnostic criteria. Cottington[11] reported that thirteen out of fifteen children, in whom the onset of the psychosis was before 10 years of age, were making reasonably good adjustments at home. Nine of these were attending regular classes at school.

The prognosis depends to a large extent on the diagnostic criteria. The earlier reports referred principally to severe cases and in these the outlook is indeed grave. But, as milder instances are being recognized, a better prognosis may be expected. The improvement which takes place is in the secondary symptoms, those centering about the anxiety, rather than in the manifestations of schizophrenia itself.

TREATMENT

Socialization.—The child should be in an institution under the care of a psychiatrist especially trained in work with children. In the institution the child, removed from the critical attitudes of the home, finds an atmosphere in which his bizarre behavior is tolerated and accepted. He is constantly stimulated to join group activities and, at the same time, he is helped and encouraged to accept reality. At the institution school he receives individual attention or he is included in small groups. He is encouraged in any special abilities which he may have and which may raise his prestige in the group. Under this regimen the child becomes less fearful and makes dependent attachments to the adults about him. A drawback to such a therapeutic approach is the intolerant attitude of other children at the institution.

Psychotherapy.—In addition to discussion with the child, play therapy, art, and the dance are used. An attempt is made to establish a relationship in which the child may feel dependent upon an adult who is at once tolerant and understanding. In this way he may be able to work out some of his problems.

Shock Therapy.—Shock therapy is used as an adjunct to socialization and psychotherapy. It may be expected, in the majority of instances, to decrease anxiety and thereby improve powers of concentration and social adaptation. Activity becomes less bizarre and less diffuse and the response to psychotherapy is better.

Work With the Parents.—An important aspect of the management of the child with schizophrenia is work with the parents. By dealing with their confusion, anxiety, and intense feelings of guilt, hostility, social isolation, and hopelessness, a positive and realistic attitude toward the child's illness may be developed. This may be best achieved to advantage by group therapy.[4] An appreciation that their plight is shared by others diminishes the parents' sense of uniqueness and helps to build relationships among the members of the group. This favors the release of previously suppressed feelings and the attainment of insight. As a result problems in the home and disturbances by the child in the neighborhood are better dealt with. The parents come to have a more sympathetic attitude toward the child and a more hopeful feeling about the outcome.

REFERENCES

1. Bradley, C.: Early Evidence of Psychosis in Children, J. PEDIAT. 30: 529, 1947.
2. Despert, J. L.: Prophylactic Aspect of Schizophrenia in Childhood, Nerv. Child 1: 199, 1942.
3. Bender, L.: Childhood Schizophrenia, Am. J. Orthopsychiat. 17: 40, 1947.
4. Peck, H. B., Rabinowitz, R. D., and Cramer, J. B.: A Treatment Program for Parents of Schizophrenic Children, Am. J. Orthopsychiat. 19: 592, 1950.
5. Despert, J. L.: The Early Recognition of Childhood Schizophrenia, Med. Clin. North America 31: 680, 1947.
6. des Lauriers, A., and Halpern, F.: Psychological Tests in Childhood Schizophrenia, Am. J. Orthopsychiat. 17: 57, 1947.
7. Werner, H., and Strauss, A.: Types of Visuo-Motor Activity in Their Relation to Low and High Performance Ages, Proc. Am. A. Ment. Deficiency 44: 163, 1939.
8. Kanner, L.: Early Infantile Autism, J. PEDIAT. 25: 211, 1944.
9. Yakovlev, P. I., Weinberger, H., and Chipman, C. E.: Heller's Syndrome as a Pattern of Schizophrenic Behavior Disorder in Early Childhood, Am. J. Ment. Deficiency 53: 2, 1948.
10. Bradley, C.: Schizophrenia in Childhood, New York, 1941, The Macmillan Company.
11. Cottington, F.: Treatment of Childhood Schizophrenia, Nerv. Child 1: 172, 1942.

Comments on Current Literature

SURGICAL TREATMENT OF COARCTATION OF THE AORTA

THIS review will call attention to a new medical journal, *Circulation*, which has been in publication since the beginning of this year. In the initial issue (January, 1950), Robert E. Gross[1] presents an excellent summary of his treatment surgically of 100 patients having coaretation of the aorta.

He prefaces the account of his own surgical experience in this field by reviewing a survey[2] of post-mortem material collected from large hospitals of the Boston area—an analysis including all findings of coaretation, regardless of whether the condition had contributed to the death. It was found that 26 per cent of such patients lived well into adult life, some to old age (the average age of death in this group was 47 years); 22 per cent of the patients died from subacute bacterial endocarditis, the average age of death, 28 years; 23 per cent of the entire group died resulting from rupture of the aorta, the average age of death, 27 years; 29 per cent died as a result of hypertension, the average age of death here, 39 years. Those patients whose death was attributable to intracranial hemorrhage as part of the hypertensive state averaged 28 years.

These statistics indicate that the prognosis of most patients with coaretation of the aorta is not good, and "prompts surgeons to attempt removal of aortic obstructions in the hope of bettering the outlook, particularly in alleviation of the hypertensive states."

The diagnosis of the condition, according to Gross, can be made in most cases without the assistance of elaborate and expensive diagnostic procedures. He points out that disparity between blood pressures in the arms and legs is of greatest importance toward detecting an aortic block. Normally, systolic pressure in the lower extremities is 20 to 40 mm. Hg higher than that in the upper extremities; in the presence of coaretation the leg pressures are far below those of the arms, and the femoral pulsations may be greatly diminished or entirely absent. Electrocardiographic tracings must be done routinely, since by this procedure essential information regarding myocardial damage or cardiac insufficiency is obtained. Even in patients within the first year of life, cardiac decompensation may occur secondary to the hypertension from aortic block. Two of eight such infants died as a result of cardiac failure, whereas the remaining six were tided over by special pediatric measures.

In discussing roentgenographic aids to diagnosis Gross concludes that "angiocardiography is not an essential part of a routine workup, but can be of value in those cases where some special interest is aroused by unusual or inexplicable findings."

In general, the author leaves the impression that coaretation of the aorta can be recognized, in most instances by simple findings of physical examination which are available to all physicians.

In view of the serious outlook for patients with coaretation—borne out by the statistics that 40 per cent of all human beings with coaretation die between the ages of 10 and 30 years and 60 per cent of all such patients die by the fortieth year—the author looks to surgical correction of the anomaly as the most important means of benefiting this group.

To date the surgical treatment which has been attempted has included four main procedures: (1) sympathectomy, (2) excision of the coaretation and anastomosis of the left subclavian artery to the distal part of the aorta, (3) removal of the coaretation and end-to-end reconstruction of the aorta, and (4) excision of the coaretation followed by insertion of an aortic graft to bridge the resulting gap. In the opinion of the author, excision of the narrowed aortic segment and reconstruction of the pathway by bringing together the remaining ends of the aortic tube is the surgical approach of greatest usefulness. Procedure 4—insertion of an aortic graft—is a comparatively new surgical technique, particularly useful in those instances where the narrowed segment is very long, and in adults in whom the remaining aorta is rigid, and the ends cannot easily be brought together.

Of the 100 patients, nine had only an exploration. There were eleven deaths either at time of operation or in the postoperative period. Four of these fatalities were regarded as unavoidable; two were regarded as avoidable deaths, one resulting from the too sudden removal of clamps at the time of operation, and one as the result of anesthesia. The remaining five fatalities were definitely associated with complicated cardiovascular conditions, such as advanced mitral stenosis, serious conduction disorders, and advanced degrees of aortic insufficiency. The operative mortality in this series of patients is 11 per cent. Gross believes that it is possible to reduce the rate in the future to 5 or 6 per cent.

During the postoperative state, study of blood pressure changes affords the best record of the readjustments which have been made in the circulatory system. The results in 80 patients who survived excision of a coaretation are as follows:

No relief of hypertension	1
Fairly satisfactory relief of hypertension	8
Complete relief of hypertension	71

The grafting of aortic segments of one human being to another is a procedure of great interest to all physicians. The author states that "the early results are quite promising in the six patients who are alive three months to one and one-half years after insertion of such grafts."

The unusual success surgeons have had in the correction of serious circulatory abnormalities should prompt the physician to search more diligently for such conditions and to provide for the surgeon the adequate medical work-up which will serve to make surgical procedures of this type less hazardous for the patient.

RUSSELL J. BLATTNER.

REFERENCES

1. Gross, R. E.: Coaretation of the Aorta, Circulation 1: 41, 1950.
2. Reifenstein, G. H., Levine, S. A., and Gross, R. E.: Coaretation of the Aorta, Am. Heart J. 33: 146, 1947.

News and Notes

The following were certified by the **American Board of Pediatrics** at the examination in San Francisco, Calif., June 30, July 1 and 2, 1950.

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Dr. Lacy George Horn Jr., The Street Clinic, Vicksburg, Miss.
Dr. Deron Hovsepian, 960 E. Green St., Pasadena 1, Calif.
Dr. Dean L. Hyde, 716 Olive Ave., Fresno, Calif.
Dr. Eugene L. Ireland, 2122 Wilshire Blvd., Santa Monica, Calif.
Dr. Herbert Livingston Kehr, 124 South Lasky Dr., Beverly Hills, Calif.
Dr. Clifford K. Kobayashi, 1415 Kalakaua Ave., Honolulu 14, Hawaii.
Dr. Fremont P. Koch, 313 S. Golden West Ave., Temple City, Calif.
Dr. Neil N. Litman, 100 W. 64th St., Inglewood, Calif.
Dr. William J. Miller, Walker Clinic, 399 E. 10th Ave., Eugene, Ore.
Dr. Percy Minden, 4418 Vineland Ave., North Hollywood, Calif.
Dr. Floyd Albert Miracle, 1531 First St., Napa, Calif.
Dr. Edwin Albert Moody, 1036 Wall St., Bend, Ore.
Dr. Jerry Newton, Medical Arts Bldg., Houston St., San Antonio, Texas.
Dr. Beulah Parker, 2886 Telegraph Ave., Berkeley, Calif.
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Dr. Naomi Kime Pitman, 139½ S. Boyle, Los Angeles, Calif.
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Dr. William Henry Wilson, 575 Fifth St., San Bernardino, Calif.
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Dr. Stanley Willard Wright, % C. W. Wright, 501 San Luis Rd., Berkeley 15, Calif.

The **American Academy of Pediatrics** and the **National Safety Council** will hold a joint meeting on Tuesday, Oct. 17, 1950, at 8 P.M. in the Grand Ballroom of the Palmer House, Chicago, Ill., to discuss methods of preventing accidents among children. The main objectives of this joint meeting are:

1. To focus national attention on the importance of child safety.
2. To develop practical methods whereby the medical profession and other safety interests can mutually aid in reducing the high accident toll among children.
3. To stimulate research in the cause and prevention of child accidents.

The following program is planned for this joint meeting:

ACCIDENTS: CHILDHOOD'S GREATEST HEALTH HAZARD

Presiding as Co-Chairman: Edward B. Shaw, M.D., President of the American Academy of Pediatrics
Ned H. Dearborn, President of the National Safety Council

Organizing for Prevention—President of the National Safety Council
The Pediatric Approach to Accident Control
a. Through practice—Harry Dietrich, M.D., Los Angeles
b. Through research—Rustin McIntosh, M.D., New York City
The Challenge of Child Accident Prevention—Dr. Herold C. Hunt, Superintendent of Schools, Chicago, Ill.

Book Reviews

Radiographic Atlas of Skeletal Development of the Hand and Wrist. William Walter Greulich, M.A., Ph.D., and S. Idell Pyle, M.S., Stanford, Calif., 1950, Stanford University Press, 190 pages. Price, $10.00.

The value and importance of skeletal growth as a measurement of the developmental status of the child has been steadily gaining recognition in recent years. In 1929, the late Dr. T. Wingate Todd of the Brush Foundation at Western Reserve University School of Medicine started on a long-term investigation of growth and development which was continued by Dr. Greulich after Dr. Todd's death in 1938. In 1937, Todd published his *Atlas of Skeletal Maturation of the Hand* which has been a standard reference book for pediatricians but is now out of print. Dr. Todd's atlas was based on material at the Research Foundation through 1936, together with films from the Cleveland area of children not a part of the study. The present atlas is composed of films from the study group of children alone, and involved the study of many thousands of films.

The first part of the atlas is devoted to a discussion of the rationale and technique of assessing the developmental status of children from roentgenograms of the hand and wrist.

It should be carefully read by everyone who attempts to use the plates for comparison with their own films.

The second section gives male standards, and the third female standards. In these sections the authors have departed from the age periods of Dr. Todd's original atlas and have lessened the number of standards presented. Plates are given for increments of 3 months of age from birth up to 18 months, then for every 6 months up to 5 years, then for each year to the beginning of puberty when the intervals are again shortened. A fourth section discusses the maturity indicators of individual bones and epiphyses.

The plates and illustrations are clear and the book is a beautiful example of the art of fine printing. It is a most valuable and a most welcome text that should be of great use to the pediatrician and should be available in every pediatric clinic and children's hospital.

Saw-Ge-Mah (Medicine Man). Louis J. Gariepy, M.D., St. Paul, Minn., 1950, Northland Press. Price $3.00.

A biographical novel of a Michigan boy who studied medicine and ended with a "group" practice. The author should have stuck to writing prescriptions.

Personality Maladjustments and Mental Hygiene. (Second Edition.) J. E. Wallace Wallen, New York, 1950, McGraw-Hill Book Company, Inc., 581 pages. Price, $5.00.

This is a revised edition presenting a systematic and comprehensive coverage of the field of mental hygiene which should be of aid to the pediatrician in understanding and coping with problems of personality maladjustment. The book is composed of seventeen chapters dealing with prevention, psychotherapeutic methods, suggestions for the handling of common personality disturbances, and others. Of particular interest to the pediatrician is Chap. 5 which is devoted entirely to a consideration of mental hygiene problems in children and Chap. 17 entitled "Suggestions From Psychoanalysis of Value in Child Guidance and Training." An excellent, up-to-date bibliographic reference list is offered.

DAVID H. KAHN.

Speech Therapy for the Physically Handicapped. Sara Stinchfield Hawk, Stanford, Calif., 1950, Stanford University Press, 245 pages. Price $4.00.

Dr. Charles LeRoy Lowman, an orthopedic surgeon, asserts in the introductory chapter of the book that "the speech teacher should not proceed singly in handling an orthopedic patient who is also a speech defective." Nine per cent of the patients in an orthopedic hospital have speech faults and should be referred to a speech therapist who will work in cooperation with the medical staff and technicians.

In the opening chapters, Dr. Hawk discusses the etiologic factors and treatment of major speech defects as referred to therapists in hospitals, university or private clinics. She stresses the importance of treating the whole child. For example, speech therapy for spastics includes relaxation, muscular exercises starting with legs and feet, then back and trunk, then hands in gesture accompanied by appropriate speech drills.

Chapters III and IV outline speech clinical methods and are filled with practical suggestions including record sheets, diagnostic speech tests, and teaching materials.

The final chapter is devoted to results of Dr. Hawk's research on fifty-three patients she has treated over an eight-year period. Familial and other environmental factors, developmental history, dental factors, educational progress, type of speech disorders, mental hygiene, and results of treatment of these selected cases are discussed.

The Appendix includes personality measurements and vocational guidance suggestions.

The book should be of interest to social workers, psychologists and members of the medical profession who are interested in speech correction as related to other hospital services for the handicapped child. The greatest value seems to be for the speech teacher seeking materials and suggestions for therapeutic procedures.

HELEN S. LANE, PH.D.

Editor's Column

WHEN POLIO BREAKS OUT IN A CAMP OR SCHOOL

WHEN a case of polio develops in a school, the school physician finds himself in a tough spot. The parents of many children, and even some of the teachers, become panicky, and the school regime and morale tend to become upset. To close or not to close becomes a moot question to the school authorities. In a similar way when a case breaks out in a summer camp or boarding school, the family physician or pediatrician is in a difficult position when his advice is sought by the parents of other children in the camp or school as to what they should do about their child. Whatever advice has been given has of necessity been the personal opinion of the physician, and sometimes the advice given to parents by one physician differs from the advice received by their friends.

The editor has a vivid recollection of the first time he faced the problem as school physician, back in 1924, when a boy in a Country Day School developed severe polio a few weeks after school opened in the fall. The disease was not prevalent in the community. The diagnosis was made the morning of the second day, and that afternoon a note was sent to every parent telling of the case, stating there was every reason to believe it was a sporadic case and not the beginning of an epidemic, that school would go on as usual, and if more cases developed the parents would be notified and the head master and school physician would take such action as they deemed to the best interests of the students. Telephone gossip and wild rumors were thus anticipated and prevented. The reaction of the parents was one of confidence in the school and only one out of some 250 boys was kept home the following day. Luckily no secondary case developed, but the school physician spent an anxious week, as the action taken was based solely on his opinion and was without a factual basis of the probabilities. Football was not stopped for a week as would have been done today. We have encountered a similar situation twice since, except that in one of the instances in a girls' school the "suspected polio" turned out to be mumps meningitis. Even more troublesome have been the more frequent occasions where polio has developed in a boarding school or camp and parents with children in the camp or school have rushed to seek advice as to what action they should take. Not knowing the exact situation has made advice difficult although it has generally been to "sit tight at present."

It was in view of these difficult situations, and of the fact that whatever advice was given had to be based on personal opinion, that we welcomed and commented editorially in THE JOURNAL last year (**35**: 526, 1949) on the report of the committee on "Recommended Practices for the Control of Poliomyelitis" of the National Foundation for Infantile Paralysis. Even if it had little scientific basis, it gave the physician something "authoritative" to fall back on in giving his opinion, and no longer left him in an isolated spot.

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A recent report by Ingalls and Rubenstein[1] of the Harvard School of Public Health on the "Expectancy for Outbreaks of Poliomyelitis in Camps and Boarding Schools" throws much information on what may be expected to take place in a camp or boarding school when an outbreak of polio occurs. It is a report with which every pediatrician should be familiar, as for the first time we have something definite to go on when the problems outlined above are encountered, and the facts should give comfort to worried parents.

Ingalls and Rubenstein obtained information on the occurrence of polio in 140 summer camps and 40 boarding schools over a fourteen-year period, 1935 to 1948. This represents nearly 2,000 summers of camp operation and 560 academic years for the schools. The period included years of high and low prevalence of the disease. Polio occurred in 30 (21 per cent) of the camps and in 12 (30 per cent) of the schools. In the 30 camps there were 21 instances where the outbreak was limited to a single case, while in 11 instances a multiple-case outbreak occurred. In the 12 schools the outbreak was limited to a single case in 11 instances, and a multiple-case outbreak occurred 3 times.

During the years 1940 to 1948 the camps had a population of 13,489 and the case rate was 0.56 per 1,000 campers. The July-August case rate for polio in Massachusetts for the same years for children 9 to 14 years of age was 0.67 per thousand. The schools during this period had a population of 12,315 and the case rate was 0.13 per 1,000 students. The case rate for children of a comparable age in Massachusetts for the academic months of the year was also 0.13 per thousand during this period. Thus the prevalence of polio among boys and girls in camps and schools corresponded in general to the incidence in the general population.

A study of the epidemiologic pattern in 53 outbreaks in the schools and camps was made. It showed that where there was a single case outbreak, no further cases developed in 35 instances, while in 7 instances 1 to 3 additional cases developed after five days. It thus appears that if the outbreak is limited to a single case in the first five days, the development of an epidemic in the camp or school would be most unusual. In 11 multiple-case outbreaks (2 or more cases in the first five days and interpreted as due to a common source) about one-half were followed by secondary cases, and from 2 to 8 per cent exposed developed the disease. In five of six outbreaks starting with 3 or more cases, the outbreak spread and in 2 instances reached epidemic proportions. It is interesting that the most extensive school outbreak occurred in May in a year of low prevalence, while the largest camp outbreak (10 cases among 122 boys) took place in a summer of high prevalence.

From these figures we have certain factual data for the first time to give to parents. As to a child in a camp or school, the chances of contracting polio are seemingly no greater than that of the child at home. If a single case develops in a school or camp the chances are 80 out of 100 there will be no further cases. In 20 per cent, 1 or 2 additional cases may be expected, but an epidemic is not likely. If the onset is multiple, the chances are that additional cases can be expected in at least one-half and epidemic proportions may be reached. The

authors have calculated that a multiple-case outbreak in an ordinary school or camp can be expected about once every century.

The authors state that the complete experience of 1949 has not been collected and analyzed, but that present information suggests the polio incidence in camps surpassed that of any year in the data presented. Likewise, a multiple-case outbreak occurred in one of the 40 schools in October, 1949. We might add that this might be expected of 1949 if the incidence in camps and schools corresponds to the general incidence.

It might be well to repeat some of the findings of the committee report referred to above, as the advice is sound. Children should not be admitted to camps or schools from an area where an outbreak exists. Boarding schools in an area where polio is prevalent should delay their opening in the fall. In general, public and private schools should not be closed during an outbreak. Children in summer camps where polio develops should be kept there for fourteen days after the last contact with a case.

With these two reports in mind, the pediatrician is in a much better situation than he has been previously to discuss the situation and advise when polio breaks out in a camp or school.

B. S. V.

REFERENCE

1. Ingalls, T. H., and Rubenstein, A. D.: Expectancy for Outbreaks of Poliomyelitis in Camps and Schools, Am. J. Pub. Health 40: 555, 1950.

LANGLEY PORTER NUMBER

THE JOURNAL for October will be dedicated to Dr. Langley Porter of San Francisco, commemorating his 80th birthday which occurred this year. In selecting contributors from among his associates, the Editorial Board has had the aid of a special editorial committee consisting of Dr. William C. Deamer, Chairman, and Drs. Orville F. Grimes, Ernest Jawetz, Salvatore P. Lucia, George H. Schade, and Henry K. Silver.

The older pediatricians are familiar with Dr. Porter's many contributions to pediatrics in the early decades of the century, and with his tremendous influence on the development of pediatrics and child health on the Pacific Coast. At the height of a brilliant pediatric career he turned to the development of the medical school of the University of California, and under his guidance as Dean it became one of the leading medical centers in the country. In honoring Dr. Porter THE JOURNAL pays tribute not only to an outstanding pediatrician and medical educator, but to a gentleman of fineness and character.

For their aid in the preparation of this special issue the Editorial Board wishes to express its indebtedness to the special editorial committee, to Dr. Porter's close friend and associate, Dr. William Carter, and to the publishers of THE JOURNAL, The C. V. Mosby Company. It has been through their help and cooperation that the special issue has developed from an idea to an actuality.